

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
21 May 2004 (21.05.2004)

PCT

(10) International Publication Number
WO 2004/041170 A2

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- (51) International Patent Classification⁷: **A61K** CA 94010 (US). **WU, Thomas, D.** [US/US]; 41 Nevada Street, San Francisco, CA 94110 (US).
- (21) International Application Number: PCT/US2003/034312 (74) Agents: **CARPENTER, David, A.** et al.; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990 (US).
- (22) International Filing Date: 30 October 2003 (30.10.2003) (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/423,394 1 November 2002 (01.11.2002) US
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- (84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— *without international search report and to be republished upon receipt of that report*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*
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(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF IMMUNE RELATED DISEASES

(57) Abstract: The present invention relates to compositions containing novel proteins and methods of using those compositions for the diagnosis and treatment of immune related diseases.

WO 2004/041170 A2

COMPOSITIONS AND METHODS FOR THE TREATMENT OF IMMUNE RELATED DISEASES

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Field of the Invention

The present invention relates to compositions and methods useful for the diagnosis and treatment of immune related diseases.

Background of the Invention

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Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

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Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

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Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases, non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, *etc.*

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Immune related diseases could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

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Macrophages represent an ubiquitously distributed population of fixed and circulating mononuclear phagocytes that express a variety of functions including cytokine production, killing of microbes and tumor cells and processing and presentation of antigens. Macrophages originate in the bone marrow from stem cells that give rise to a bipotent granulocyte/macrophage cell population. Distinct granulocyte and macrophage colony forming cell lineages arise from GM-CSF under the influence of specific cytokines. Upon division, monoblasts give rise to promonocytes and monocytes in the bone marrow. From there, monocytes enter the circulation. In response to particular stimuli (e.g. infection or foreign bodies) monocytes migrate into tissues and organs where they differentiate into macrophages.

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Macrophages in various tissues vary in their morphology and function and have been assigned different names, e.g. Kupffer cells in the liver, pulmonary and alveolar macrophages in the lung and microglial cells in the central nervous system. However, the relationship between blood monocytes and tissue macrophages remains unclear.

In the present study monocytes were differentiated into macrophages by adherence to plastic in the presence of a combination of human and bovine serum. After 7 days in culture, monocytes-derived macrophages display features typical of differentiated tissue macrophages including their ability to phagocytose opsonized particles, secretion of TNF-alpha upon lipopolysaccharide (LPS) stimulation, formation of processes and the presence of macrophage cell surface markers.

Using microarray technologies, gene transcripts from non-differentiated monocytes harvested before adhering were compared with those at 1 day and 7 days in culture. Genes selectively expressed in monocytes or macrophages could be used for the diagnosis and treatment of various chronic inflammatory or autoimmune diseases in the human. In particular, surface expressed molecules or transmembrane receptors involved in monocyte/macrophage adhesion and endothelial cell transmigration could provide novel targets to treat chronic inflammation by interference with the homing of these cells to the site of inflammation. In addition, transmembrane inhibitory receptors could be used to down-regulate monocyte/macrophage effector functions. Therapeutic molecules can be antibodies, peptides, fusion proteins or small molecules.

Despite the above research in monocyte/macrophages, there is a great need for additional diagnostic and therapeutic agents capable of detecting the presence of monocyte/macrophage mediated disorders in a mammal and for effectively reducing these disorders. Accordingly, it is an objective of the present invention to identify polypeptides that are differentially expressed in macrophages as compared to non-differentiated monocytes, and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of monocyte/macrophage mediated disorders in mammals.

Summary of the Invention

A. Embodiments

The present invention concerns compositions and methods useful for the diagnosis and treatment of immune related disease in mammals, including humans. The present invention is based on the identification of proteins (including agonist and antagonist antibodies) which are a result of stimulation of the immune response in mammals. Immune related diseases can be treated by suppressing or enhancing the immune response. Molecules that enhance the immune response stimulate or potentiate the immune response to an antigen. Molecules which stimulate the immune response can be used therapeutically where enhancement of the immune response would be beneficial. Alternatively, molecules that suppress the immune response attenuate or reduce the immune response to an antigen (*e.g.*, neutralizing antibodies) can be used therapeutically where attenuation of the immune response would be beneficial (*e.g.*, inflammation). Accordingly, the PRO polypeptides, agonists and antagonists thereof are also useful to prepare medicines and medicaments for the treatment of immune-related and inflammatory diseases. In a specific aspect, such medicines and medicaments comprise a therapeutically effective amount of a PRO polypeptide, agonist or antagonist thereof with a pharmaceutically acceptable carrier. Preferably, the admixture is sterile.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprises contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a

native sequence PRO polypeptide. In a specific aspect, the PRO agonist or antagonist is an anti-PRO antibody.

In another embodiment, the invention concerns a composition of matter comprising a PRO polypeptide or an agonist or antagonist antibody which binds the polypeptide in admixture with a carrier or excipient. In one aspect, the composition comprises a therapeutically effective amount of the polypeptide or antibody. In another aspect, when the composition comprises an immune stimulating molecule, the composition is useful for: (a) increasing infiltration of inflammatory cells into a tissue of a mammal in need thereof, (b) stimulating or enhancing an immune response in a mammal in need thereof, (c) increasing the proliferation of monocytes/macrophages in a mammal in need thereof in response to an antigen, (d) stimulating the activity of monocytes/macrophages or (e) increasing the vascular permeability. In a further aspect, when the composition comprises an immune inhibiting molecule, the composition is useful for: (a) decreasing infiltration of inflammatory cells into a tissue of a mammal in need thereof, (b) inhibiting or reducing an immune response in a mammal in need thereof, (c) decreasing the activity of monocytes/macrophages or (d) decreasing the proliferation of monocytes/macrophages in a mammal in need thereof in response to an antigen. In another aspect, the composition comprises a further active ingredient, which may, for example, be a further antibody or a cytotoxic or chemotherapeutic agent. Preferably, the composition is sterile.

In another embodiment, the invention concerns a method of treating an immune related disorder in a mammal in need thereof, comprising administering to the mammal an effective amount of a PRO polypeptide, an agonist thereof, or an antagonist thereto. In a preferred aspect, the immune related disorder is selected from the group consisting of: systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis, idiopathic inflammatory myopathies, Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious, autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft -versus-host-disease.

In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody. In one aspect, the present invention concerns an isolated antibody which binds a PRO polypeptide. In another aspect, the antibody mimics the activity of a PRO polypeptide (an agonist antibody) or conversely the antibody inhibits or neutralizes the activity of a PRO polypeptide (an antagonist antibody). In another aspect, the antibody is a monoclonal antibody, which preferably has nonhuman complementarity determining region (CDR) residues and human framework region

(FR) residues. The antibody may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a monoclonal antibody, a single-chain antibody, or an anti-idiotypic antibody.

In yet another embodiment, the present invention provides a composition comprising an anti-PRO antibody in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition comprises a therapeutically effective amount of the antibody. Preferably, the composition is sterile. The composition may be administered in the form of a liquid pharmaceutical formulation, which may be preserved to achieve extended storage stability. Alternatively, the antibody is a monoclonal antibody, an antibody fragment, a humanized antibody, or a single-chain antibody.

In a further embodiment, the invention concerns an article of manufacture, comprising:

- (a) a composition of matter comprising a PRO polypeptide or agonist or antagonist thereof;
- (b) a container containing said composition; and
- (c) a label affixed to said container, or a package insert included in said container referring to the use of said PRO polypeptide or agonist or antagonist thereof in the treatment of an immune related disease. The composition may comprise a therapeutically effective amount of the PRO polypeptide or the agonist or antagonist thereof.

In yet another embodiment, the present invention concerns a method of diagnosing an immune related disease in a mammal, comprising detecting the level of expression of a gene encoding a PRO polypeptide (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower expression level in the test sample as compared to the control sample indicates the presence of immune related disease in the mammal from which the test tissue cells were obtained.

In another embodiment, the present invention concerns a method of diagnosing an immune disease in a mammal, comprising (a) contacting an anti-PRO antibody with a test sample of tissue cells obtained from the mammal, and (b) detecting the formation of a complex between the antibody and a PRO polypeptide, in the test sample; wherein the formation of said complex is indicative of the presence or absence of said disease. The detection may be qualitative or quantitative, and may be performed in comparison with monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger quantity of complexes formed in the test sample indicates the presence or absence of an immune disease in the mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. The test sample is usually obtained from an individual suspected of having a deficiency or abnormality of the immune system.

In another embodiment, the invention provides a method for determining the presence of a PRO polypeptide in a sample comprising exposing a test sample of cells suspected of containing the PRO polypeptide to an anti-PRO antibody and determining the binding of said antibody to said cell sample. In a specific aspect, the sample comprises a cell suspected of containing the PRO polypeptide and the antibody binds to the cell. The antibody is preferably detectably labeled and/or bound to a solid support.

In another embodiment, the present invention concerns an immune-related disease diagnostic kit, comprising an anti-PRO antibody and a carrier in suitable packaging. The kit preferably contains

instructions for using the antibody to detect the presence of the PRO polypeptide. Preferably the carrier is pharmaceutically acceptable.

In another embodiment, the present invention concerns a diagnostic kit, containing an anti-PRO antibody in suitable packaging. The kit preferably contains instructions for using the antibody to detect the PRO polypeptide.

In another embodiment, the invention provides a method of diagnosing an immune-related disease in a mammal which comprises detecting the presence or absence of a PRO polypeptide in a test sample of tissue cells obtained from said mammal, wherein the presence or absence of the PRO polypeptide in said test sample is indicative of the presence of an immune-related disease in said mammal.

In another embodiment, the present invention concerns a method for identifying an agonist of a PRO polypeptide comprising:

(a) contacting cells and a test compound to be screened under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

(b) determining the induction of said cellular response to determine if the test compound is an effective agonist, wherein the induction of said cellular response is indicative of said test compound being an effective agonist.

In another embodiment, the invention concerns a method for identifying a compound capable of inhibiting the activity of a PRO polypeptide comprising contacting a candidate compound with a PRO polypeptide under conditions and for a time sufficient to allow these two components to interact and determining whether the activity of the PRO polypeptide is inhibited. In a specific aspect, either the candidate compound or the PRO polypeptide is immobilized on a solid support. In another aspect, the non-immobilized component carries a detectable label. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

(b) determining the induction of said cellular response to determine if the test compound is an effective antagonist.

In another embodiment, the invention provides a method for identifying a compound that inhibits the expression of a PRO polypeptide in cells that normally express the polypeptide, wherein the method comprises contacting the cells with a test compound and determining whether the expression of the PRO polypeptide is inhibited. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened under conditions suitable for allowing expression of the PRO polypeptide; and

(b) determining the inhibition of expression of said polypeptide.

In yet another embodiment, the present invention concerns a method for treating an immune-related disorder in a mammal that suffers therefrom comprising administering to the mammal a nucleic acid molecule that codes for either (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide or (c) an antagonist of a PRO polypeptide, wherein said agonist or antagonist may be an anti-PRO antibody. In a preferred embodiment, the mammal is human. In another preferred embodiment, the nucleic acid is administered via *ex vivo* gene therapy. In a further preferred embodiment, the nucleic acid is comprised within a vector, more preferably an adenoviral, adeno-associated viral, lentiviral or retroviral vector.

In yet another aspect, the invention provides a recombinant viral particle comprising a viral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide, or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein the viral vector is in association with viral structural proteins.

5 Preferably, the signal sequence is from a mammal, such as from a native PRO polypeptide.

In a still further embodiment, the invention concerns an *ex vivo* producer cell comprising a nucleic acid construct that expresses retroviral structural proteins and also comprises a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular
10 secretion of the polypeptide, wherein said producer cell packages the retroviral vector in association with the structural proteins to produce recombinant retroviral particles.

In a still further embodiment, the invention provides a method of increasing the activity of monocytes/macrophages in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the activity of
15 monocytes/macrophages in the mammal is increased.

In a still further embodiment, the invention provides a method of decreasing the activity of monocytes/macrophages in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the activity of
monocytes/macrophages in the mammal is decreased.

20 In a still further embodiment, the invention provides a method of increasing the proliferation of monocytes/macrophages in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the proliferation of monocytes/macrophages in the mammal is increased.

In a still further embodiment, the invention provides a method of decreasing the proliferation of
25 monocytes/macrophages in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the proliferation of monocytes/macrophages in the mammal is decreased.

B. Additional Embodiments

In other embodiments of the present invention, the invention provides vectors comprising DNA
30 encoding any of the herein described polypeptides. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

35 In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences.

In other embodiments, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an

extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 20 nucleotides in length, alternatively at least about 30 nucleotides in length, alternatively at least about 40 nucleotides in length, alternatively at least about 50 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 70 nucleotides in length, alternatively at least about 80 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 100 nucleotides in length, alternatively at least about 110 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 130 nucleotides in length, alternatively at least about 140 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 160 nucleotides in length, alternatively at least about 170 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 190 nucleotides in length, alternatively at least about 200 nucleotides in length, alternatively at least about 250 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 350 nucleotides in length, alternatively at least about 400 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 500 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 700

nucleotides in length, alternatively at least about 800 nucleotides in length, alternatively at least about 900 nucleotides in length and alternatively at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

In another embodiment, the invention provides isolated PRO polypeptide encoded by any of the isolated nucleic acid sequences herein above identified.

In a certain aspect, the invention concerns an isolated PRO polypeptide, comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid

sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as herein before described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention concerns a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as herein before described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

In the list of figures for the present application, specific cDNA sequences which are differentially expressed in differentiated macrophages as compared to normal undifferentiated monocytes are individually identified with a specific alphanumerical designation. These cDNA sequences are differentially expressed in monocytes that are specifically treated as described in Example 1 below. If start and/or stop codons have been identified in a cDNA sequence shown in the attached figures, they are shown in bold and underlined font, and the encoded polypeptide is shown in the next consecutive figure.

The Figures 1-2517 show the nucleic acids of the invention and their encoded PRO polypeptides. Also included, for convenience is a List of Figures attached hereto as Appendix A, which gives the figure number and the corresponding DNA or PRO number.

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 Figure 29: DNA328353, AAB72234.1, 37079_at
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 Figure 31: DNA103289, NP_006229.1, 37152_at
 Figure 32: PRO4619
 Figure 33A-B: DNA255096, NP_055449.1, 37384_at
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 Figure 35: DNA256295, NP_002310.1, 37796_at
 Figure 36: PRO51339
 Figure 37: DNA328354, PARVB, 37965_at
 Figure 38: PRO84215
 Figure 39: DNA53531, NP_001936.1, 38037_at
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 Figure 41: DNA254127, NP_008925.1, 38241_at
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 Figure 45: DNA328356, BC013566, 39248_at
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 Figure 47: DNA328357, 1452321.2, 39582_at
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 Figure 49A-B: DNA328358, STK10, 40420_at
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 Figure 51A-B: DNA328359, BAA21572.1, 41386_i_at
 Figure 52: PRO84219
 Figure 53A-D: DNA328360, NP_055061.1, 41660_at
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 Figure 55: DNA327526, BC001698, 45288_at
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 Figure 57A-B: DNA328361, BAA92570.1, 47773_at
 Figure 58: PRO84221
 Figure 59: DNA328362, NP_060312.1, 48106_at
 Figure 60: PRO84222
 Figure 61: DNA328363, DNA328363, 52651_at
 Figure 62: PRO84685
 Figure 63: DNA328364, NP_068577.1, 52940_at
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 Figure 65A-B: DNA327528, BAB33338.1, 55081_at
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 Figure 67: DNA225650, NP_057246.1, 48825_at
 Figure 68: PRO36113
 Figure 69: DNA328365, NP_060541.1, 58780_s_at
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 Figure 78: PRO84227
 Figure 79: DNA328369, BC007634, 90610_at
 Figure 80A-B: DNA328370, NP_001273.1, 200615_s_at
 Figure 81: PRO84228
 Figure 82: DNA323806, NP_075385.1, 200644_at
 Figure 83: PRO80555
 Figure 84: DNA327532, GLUL, 200648_s_at
 Figure 85: PRO71134
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 Figure 87: PRO37518
 Figure 88: DNA325702, NP_001771.1, 200663_at
 Figure 89: PRO283
 Figure 90: DNA83172, NP_003109.1, 200665_s_at
 Figure 91: PRO2120
 Figure 92: DNA328371, NP_004347.1, 200675_at
 Figure 93: PRO4866
 Figure 94A-B: DNA328372, 105551.7, 200685_at
 Figure 95: PRO84229
 Figure 96: DNA324633, BC000478, 200691_s_at
 Figure 97: PRO81277
 Figure 98: DNA324633, NP_004125.2, 200692_s_at
 Figure 99: PRO81277
 Figure 100: DNA88350, NP_000168.1, 200696_s_at
 Figure 101: PRO2758
 Figure 102: DNA328373, AB034747, 200704_at
 Figure 103: PRO84230
 Figure 104: DNA328374, NP_004853.1, 200706_s_at
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 Figure 106: DNA328375, NP_002071.1, 200708_at
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Figure 109: PRO1015
Figure 110A-B: DNA269826, NP_003195.1, 200758_s.at
Figure 111: PRO58228
Figure 112: DNA325414, NP_001900.1, 200766_at
Figure 113: PRO292
Figure 114A-C: DNA188738, NP_002284.2, 200771_at
Figure 115: PRO25580
Figure 116: DNA328377, NP_003759.1, 200787_s.at
Figure 117: PRO84232
Figure 118: DNA270954, NP_001089.1, 200793_s.at
Figure 119: PRO59285
Figure 120: DNA272928, NP_055579.1, 200794_x.at
Figure 121: PRO61012
Figure 122A-B: DNA327536, BC017197, 200797_s.at
Figure 123: PRO37003
Figure 124: DNA287211, NP_002147.1, 200806_s.at
Figure 125: PRO69492
Figure 126: DNA326655, NP_002803.1, 200820_at
Figure 127: PRO83005
Figure 128A-B: DNA328378, AB032261, 200832_s.at
Figure 129: PRO84233
Figure 130: DNA103558, NP_005736.1, 200837_at
Figure 131: PRO4885
Figure 132: DNA196817, NP_001899.1, 200838_at
Figure 133: PRO3344
Figure 134A-B: DNA327537, NP_004437.1, 200842_s.at
Figure 135: PRO83581
Figure 136: DNA323982, NP_004896.1, 200844_s.at
Figure 137: PRO80709
Figure 138: DNA323876, NP_006612.2, 200850_s.at
Figure 139: PRO80619
Figure 140A-B: DNA228029, NP_055577.1, 200862_at
Figure 141: PRO38492
Figure 142: DNA328379, BC015869, 200878_at
Figure 143: PRO84234
Figure 144: DNA325584, NP_002005.1, 200895_s.at
Figure 145: PRO59262
Figure 146A-B: DNA274281, NP_036347.1, 200899_s.at
Figure 147: PRO62204
Figure 148: DNA226028, NP_002346.1, 200900_s.at
Figure 149: PRO36491
Figure 150: DNA326819, NP_000678.1, 200903_s.at
Figure 151: PRO83152
Figure 152: DNA328380, HSHLAEHCM, 200904_at
Figure 153: DNA328381, NP_005507.1, 200905_x.at
Figure 154: PRO84236
Figure 155: DNA272695, NP_001722.1, 200920_s.at
Figure 156: PRO60817
Figure 157: DNA327255, NP_002385.2, 200924_s.at
Figure 158: PRO57298
Figure 159: DNA327540, NP_006818.1, 200929_at
Figure 160: PRO38005
Figure 161: DNA225878, NP_004334.1, 200935_at
Figure 162: PRO36341
Figure 163: DNA328382, 160963.2, 200941_at
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Figure 168: PRO36766
Figure 169: DNA328384, NP_036380.2, 200961_at
Figure 170: PRO84239
Figure 171: DNA328385, AK001310, 200972_at
Figure 172: PRO730
Figure 173: DNA326040, NP_005715.1, 200973_s.at
Figure 174: PRO730
Figure 175: DNA324110, NP_005908.1, 200978_at
Figure 176: PRO4918
Figure 177: DNA328386, NP_000602.1, 200983_x.at
Figure 178: PRO2697
Figure 179: DNA275408, NP_001596.1, 201000_at
Figure 180: PRO63068
Figure 181: DNA328387, NP_001760.1, 201005_at
Figure 182: PRO4769
Figure 183: DNA103593, NP_000174.1, 201007_at
Figure 184: PRO4917
Figure 185: DNA304713, NP_006463.2, 201008_s.at
Figure 186: PRO71139
Figure 187: DNA328388, BC010273, 201013_s.at
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Figure 189: DNA328389, NP_006861.1, 201021_s.at
Figure 190: PRO84241
Figure 191: DNA328390, NP_002291.1, 201030_x.at
Figure 192: PRO82116
Figure 193: DNA196628, NP_005318.1, 201036_s.at
Figure 194: PRO25105
Figure 195: DNA287372, NP_002618.1, 201037_at
Figure 196: PRO69632
Figure 197: DNA328391, NP_004408.1, 201041_s.at
Figure 198: PRO84242
Figure 199: DNA196484, DNA196484, 201042_at
Figure 200: DNA227143, NP_036400.1, 201050_at
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Figure 202: DNA328392, 1500938.11, 201051_at
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Figure 204: DNA328261, AF130103, 201060_x.at
Figure 205: DNA325001, NP_002794.1, 201068_s.at
Figure 206: PRO81592
Figure 207: DNA328393, NP_001651.1, 201096_s.at
Figure 208: PRO81010
Figure 209: DNA328394, AF131738, 201103_x.at
Figure 210A-B: DNA328395, NP_056198.1, 201104_x.at
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Figure 212: DNA328396, NP_002076.1, 201106_at
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Figure 214: DNA328397, NP_002622.1, 201118_at

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 Figure 216: DNA328398, NP_002204.1, 201125.s_at
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 Figure 218: DNA325398, NP_004083.2, 201135.at
 Figure 219: PRO81930
 Figure 220: DNA88520, NP_002501.1, 201141.at
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 Figure 222: DNA324480, NP_001544.1, 201163.s_at
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 Figure 224: DNA151802, NP_003661.1, 201169.s_at
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 Figure 228: DNA88066, NP_002328.1, 201186.at
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 Figure 231: PRO61345
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 Figure 243A-B: DNA328402, NP_073713.1, 201220.x_at
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 Figure 245: DNA325380, NP_004995.1, 201226.at
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 Figure 248: PRO37078
 Figure 249: DNA328403, NP_037462.1, 201243.s_at
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 Figure 251: DNA270950, NP_003182.1, 201263.at
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 Figure 255: DNA97290, NP_002503.1, 201268.at
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 Figure 258: PRO81617
 Figure 259: DNA328405, NP_112556.1, 201277.s_at
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 Figure 261: DNA328406, NP_001334.1, 201279.s_at
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 Figure 267: DNA325595, NP_001966.1, 201313.at
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 Figure 273: DNA328409, NP_002075.2, 201348.at
 Figure 274: PRO81281
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 Figure 276: PRO81137
 Figure 277: DNA226353, NP_005769.1, 201395.at
 Figure 278: PRO36816
 Figure 279: DNA328410, NP_004519.1, 201403.s_at
 Figure 280: PRO60174
 Figure 281A-B: DNA328411, 1400253.2, 201408.at
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 Figure 283: DNA328412, NP_060428.1, 201411.s_at
 Figure 284: PRO84257
 Figure 285: DNA273517, NP_000169.1, 201415.at
 Figure 286: PRO61498
 Figure 287: DNA327550, NP_001959.1, 201435.s_at
 Figure 288: PRO81164
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 Figure 296: DNA328414, NP_003891.1, 201471.s_at
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 Figure 300: DNA88608, NP_002893.1, 201485.s_at
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 Figure 304: DNA304459, NP_005720.1, 201490.s_at
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 Figure 306: DNA253807, NP_065390.1, 201502.s_at
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 Figure 308: DNA328415, BC006997, 201503.at
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 Figure 312: DNA271931, NP_005745.1, 201514.s_at
 Figure 313: PRO60207
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 Figure 317: PRO84260
 Figure 318: DNA328418, NP_003398.1, 201531.at
 Figure 319: PRO84261
 Figure 320: DNA328419, NP_002779.1, 201532.at
 Figure 321: PRO84262
 Figure 322: DNA328420, BC002682, 201537.s_at
 Figure 323: PRO58245
 Figure 324: DNA88464, NP_005552.2, 201551.s_at

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Figure 327: PRO70317
Figure 328: DNA227071, NP_000260.1, 201577_at
Figure 329: PRO37534
Figure 330A-B: DNA227307, NP_009115.1, 201591.s_at
Figure 331: PRO37770
Figure 332: DNA255406, NP_005533.1, 201625.s_at
Figure 333: PRO50473
Figure 334A-B: DNA328421, 475621.10, 201646_at
Figure 335: PRO51048
Figure 336A-B: DNA220748, NP_000201.1, 201656_at
Figure 337: PRO34726
Figure 338: DNA269791, NP_001168.1, 201659.s_at
Figure 339: PRO58197
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Figure 345: PRO61148
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Figure 347: PRO59291
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Figure 353: PRO59218
Figure 354A-B: DNA328425, NP_065207.2, 201722.s_at
Figure 355: PRO84264
Figure 356: DNA328426, NP_000582.1, 201743_at
Figure 357: PRO384
Figure 358: DNA150429, NP_002813.1, 201745_at
Figure 359: PRO12769
Figure 360: DNA272465, NP_004543.1, 201757_at
Figure 361: PRO60713
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Figure 366: DNA323937, NP_005689.2, 201771_at
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Figure 368: DNA88619, NP_002924.1, 201785_at
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Figure 370A-B: DNA328428, NP_038479.1, 201798.s_at
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Figure 374: DNA225896, NP_000109.1, 201808.s_at
Figure 375: PRO36359
Figure 376: DNA151017, NP_004835.1, 201810.s_at
Figure 377: PRO12841
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Figure 379: PRO81201
Figure 380: DNA328430, NP_005496.2, 201819_at
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Figure 384: DNA150650, NP_057086.1, 201825.s_at
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Figure 390: DNA150725, NP_001738.1, 201850_at
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Figure 398: DNA227112, NP_006397.1, 201923_at
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Figure 403: PRO61085
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Figure 405: PRO49262
Figure 406: DNA274167, NP_006422.1, 201946.s_at
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Figure 411: DNA227290, NP_055861.1, 201965.s_at
Figure 412: PRO37753
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Figure 414: PRO61793
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Figure 416: PRO84268
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Figure 420: PRO37341
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Figure 423: DNA328435, NP_002481.1, 202001.s_at
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Figure 425: DNA275246, NP_006102.1, 202003.s_at
Figure 426: PRO62933
Figure 427: DNA327841, NP_068813.1, 202005_at
Figure 428: PRO12377

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Figure 565: DNA84130, NP_003801.1, 202687.s_at
Figure 566: PRO1096
Figure 567: DNA271085, NP_004751.1, 202693.s_at
Figure 568: PRO59409
Figure 569A-B: DNA150467, NP_055513.1, 202699.s_at
Figure 570: PRO12272
Figure 571A-B: DNA328459, NP_004332.2, 202715.at
Figure 572: PRO84285
Figure 573: DNA273290, NP_002047.1, 202722.s_at
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Figure 575: DNA328460, NP_004190.1, 202733.at
Figure 576: PRO84286
Figure 577: DNA150713, NP_006570.1, 202735.at
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Figure 581: DNA271973, NP_002722.1, 202742.s_at
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Figure 583A-B: DNA150943, NP_036376.1, 202752.x_at
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Figure 586: PRO84288
Figure 587A-C: DNA328463, NP_009134.1, 202760.s_at
Figure 588: PRO84289
Figure 589: DNA226080, NP_001601.1, 202767.at
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Figure 591A-B: DNA150977, NP_006723.1, 202768.at
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Figure 593A-B: DNA328464, 977954.20, 202769.at
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Figure 601: DNA328465, NP_005639.1, 202823.at
Figure 602: PRO84291
Figure 603: DNA225865, NP_004986.1, 202827.s_at
Figure 604: PRO36328
Figure 605: DNA225926, NP_000138.1, 202838.at
Figure 606: PRO36389
Figure 607: DNA328466, NP_004554.1, 202847.at
Figure 608: PRO84292
Figure 609: DNA103394, NP_004198.1, 202855.s_at
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Figure 611: DNA275144, NP_000128.1, 202862.at
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Figure 613: DNA328467, SP100, 202864.s_at
Figure 614: PRO84293
Figure 615: DNA287289, NP_058132.1, 202869.at
Figure 616: PRO69559
Figure 617: DNA328468, BC010960, 202872.at
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Figure 624: PRO84296
Figure 625: DNA327584, NP_002955.2, 202917.s_at
Figure 626: PRO80649
Figure 627: DNA272425, NP_001489.1, 202923.s_at
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Figure 629: DNA328471, ZMPSTE24, 202939.at
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Figure 633: DNA328472, NP_000482.2, 202953.at
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Figure 635A-B: DNA328473, NP_006473.1,

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Figure 636: PRO84299
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Figure 639: DNA325915, ZAP128, 202982.s_at
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Figure 642: PRO59583
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Figure 645A-B: DNA271865, NP_055566.1, 203037.s_at
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Figure 647: DNA328475, LAMP2, 203042.at
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Figure 649A-B: DNA328476, AF074331, 203058.s_at
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Figure 651: DNA256830, NP_004815.1, 203100.s_at
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Figure 659A-B: DNA328478, NP_055720.2, 203158.s_at
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Figure 665A-C: DNA328480, NP_001990.1, 203184.at
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Figure 667A-B: DNA271010, NP_055552.1, 203185.at
Figure 668: PRO59339
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Figure 672: PRO84307
Figure 673A-C: DNA328482, NP_000426.1, 203238.s_at
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Figure 675: DNA328483, NP_061163.1, 203255.at
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Figure 679: DNA328484, UNC119, 203271.s_at
Figure 680: PRO84310
Figure 681: DNA302020, NP_005564.1, 203276.at
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Figure 700: PRO84316
Figure 701: DNA328493, NP_008957.1, 203367.at
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Figure 706: PRO62694
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 Figure 1064: DNA328569, NP_077274.1, 205634_x_at
 Figure 1065: PRO84365
 Figure 1066: DNA88076, NP_001628.1, 205639_at
 Figure 1067: PRO2640
 Figure 1068: DNA287317, NP_003724.1, 205660_at
 Figure 1069: PRO69582
 Figure 1070: DNA328570, NP_004040.1, 205681_at
 Figure 1071: PRO37843
 Figure 1072: DNA327644, NP_060395.2, 205684_s_at
 Figure 1073: PRO83645
 Figure 1074: DNA150621, NP_036595.1, 205704_s_at
 Figure 1075: PRO12374
 Figure 1076: DNA328571, NP_001254.1, 205709_s_at
 Figure 1077: PRO84366
 Figure 1078: DNA88106, NP_004325.1, 205715_at
 Figure 1079: PRO2655
 Figure 1080: DNA270401, NP_003140.1, 205743_at
 Figure 1081: PRO58784
 Figure 1082: DNA275620, NP_000628.1, 205770_at
 Figure 1083: PRO63244
 Figure 1084: DNA88187, NP_001757.1, 205789_at
 Figure 1085: PRO2689
 Figure 1086: DNA76517, NP_002176.1, 205798_at
 Figure 1087: PRO2541
 Figure 1088A-B: DNA271915, NP_056191.1, 205801_s_at
 Figure 1089: PRO60192
 Figure 1090: DNA194766, NP_079504.1, 205804_s_at
 Figure 1091: PRO24046
 Figure 1092: DNA328572, NP_004309.2, 205808_at
 Figure 1093: PRO84367
 Figure 1094: DNA328573, NP_006761.1, 205819_at
 Figure 1095: PRO1559
 Figure 1096A-B: DNA328574, NP_004963.1, 205842_s_at
 Figure 1097: PRO84368
 Figure 1098: DNA327651, NP_005612.1, 205863_at
 Figure 1099: PRO83649
 Figure 1100: DNA328575, NP_071754.2, 205872_x_at
 Figure 1101: PRO84369
 Figure 1102A-B: DNA220746, NP_000876.1, 205884_at
 Figure 1103: PRO34724
 Figure 1104A-B: DNA273962, NP_055605.1, 205888_s_at
 Figure 1105: PRO61910
 Figure 1106: DNA93423, NP_000667.1, 205891_at
 Figure 1107: PRO4944
 Figure 1108: DNA328576, HSU20350, 205898_at
 Figure 1109: PRO4940
 Figure 1110: DNA328577, NP_003905.1, 205899_at
 Figure 1111: PRO59588
 Figure 1112A-B: DNA196549, NP_003034.1, 205920_at
 Figure 1113: PRO25031
 Figure 1114: DNA328578, NP_004656.2, 205922_at
 Figure 1115: PRO7426
 Figure 1116A-B: DNA270867, NP_006217.1, 205934_at
 Figure 1117: PRO59203
 Figure 1118: DNA76516, NP_000556.1, 205945_at
 Figure 1119: PRO2022
 Figure 1120: DNA196439, NP_003865.1, 205988_at
 Figure 1121: PRO24934
 Figure 1122: DNA36722, NP_000576.1, 205992_s_at
 Figure 1123: PRO77
 Figure 1124: DNA328579, BC020082, 206020_at
 Figure 1125: PRO84370
 Figure 1126: DNA328580, HSU27699, 206058_at
 Figure 1127: PRO4627
 Figure 1128: DNA328581, NP_002122.1, 206074_s_at
 Figure 1129: PRO34536
 Figure 1130: DNA328582, NP_001865.1, 206100_at
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 Figure 1132: DNA226105, NP_002925.1, 206111_at
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 Figure 1135: PRO36227
 Figure 1136: DNA328583, ASGR2, 206130_s_at
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 Figure 1138: DNA327656, NP_055294.1, 206134_at
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 Figure 1140A-B: DNA271837, NP_055497.1, 206135_at
 Figure 1141: PRO60117
 Figure 1142: DNA328584, NP_001148.1, 206200_s_at
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 Figure 1146: DNA218691, NP_003832.1, 206222_at
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 Figure 1148A-C: DNA328585, AF286028, 206239_s_at
 Figure 1149: DNA328586, NP_002369.2, 206267_s_at
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 Figure 1153: DNA255814, NP_005840.1, 206420_at
 Figure 1154: PRO50869
 Figure 1155: DNA328588, NP_060823.1, 206500_s_at
 Figure 1156: PRO84374
 Figure 1157: DNA270444, NP_004824.1, 206513_at
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Figure 1162: PRO58414
Figure 1163: DNA327663, NP_006771.1, 206565.x_at
Figure 1164: PRO83654
Figure 1165: DNA327665, NP_002099.1, 206643.at
Figure 1166: PRO83655
Figure 1167: DNA328589, BCL2L1, 206665.s_at
Figure 1168: PRO83141
Figure 1169: DNA328590, C6orf32, 206707.x_at
Figure 1170: PRO84375
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Figure 1172: PRO2691
Figure 1173: DNA327669, NP_000914.1, 206792.x_at
Figure 1174: PRO83657
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Figure 1176: PRO58498
Figure 1177: DNA256561, NP_062550.1, 206914.at
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Figure 1179: DNA328591, NP_006635.1, 206976.s_at
Figure 1180: PRO84376
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Figure 1182: PRO38122
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Figure 1184: PRO21820
Figure 1185: DNA328592, AB015228, 207016.s_at
Figure 1186: PRO84377
Figure 1187: DNA227531, NP_004722.1, 207057.at
Figure 1188: PRO37994
Figure 1189: DNA327673, NP_002188.1, 207071.s_at
Figure 1190: PRO83660
Figure 1191A-B: DNA328593, CIAS1, 207075.at
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Figure 1193A-B: DNA328594, CSF1, 207082.at
Figure 1194: PRO84379
Figure 1195: DNA88291, NP_001965.1, 207111.at
Figure 1196: PRO2729
Figure 1197A-B: DNA327674, NP_002739.1, 207121.s_at
Figure 1198: PRO83661
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Figure 1200: PRO84380
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Figure 1202: PRO37459
Figure 1203A-B: DNA226536, NP_003225.1, 207332.s_at
Figure 1204: PRO36999
Figure 1205: DNA227668, NP_000158.1, 207387.s_at
Figure 1206: PRO38131
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Figure 1208: PRO37741
Figure 1209: DNA274829, NP_003653.1, 207469.s_at
Figure 1210: PRO62588
Figure 1211: DNA328597, NP_001680.1, 207507.s_at
Figure 1212: PRO84381
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Figure 1214: PRO23276
Figure 1215: DNA328599, NFKB2, 207535.s_at
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Figure 1217: DNA328600, NP_004839.1, 207571.x_at
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Figure 1220: PRO84384
Figure 1221: DNA328602, NP_002261.1, 207657.x_at
Figure 1222: PRO84385
Figure 1223: DNA226278, NP_005865.1, 207697.x_at
Figure 1224: PRO36741
Figure 1225: DNA227395, NP_005331.1, 207721.x_at
Figure 1226: PRO37858
Figure 1227: DNA325654, NP_054752.1, 207761.s_at
Figure 1228: PRO4348
Figure 1229: DNA226930, NP_004152.1, 207791.s_at
Figure 1230: PRO37393
Figure 1231: DNA328603, NP_000304.1, 207808.s_at
Figure 1232: PRO84386
Figure 1233: DNA328604, NP_001174.2, 207809.s_at
Figure 1234: PRO84387
Figure 1235: DNA327682, NP_001905.1, 207843.x_at
Figure 1236: PRO83666
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Figure 1239: DNA199788, NP_002981.1, 207861.at
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Figure 1242: PRO84388
Figure 1243: DNA256523, NP_006854.1, 207872.s_at
Figure 1244: PRO51557
Figure 1245: DNA218651, NP_003798.1, 207907.at
Figure 1246: PRO34447
Figure 1247: DNA275286, NP_009205.1, 208002.s_at
Figure 1248: PRO62967
Figure 1249A-B: DNA328606, CBFA2T3, 208056.s_at
Figure 1250: PRO84389
Figure 1251A-B: DNA328607, NP_003639.1, 208072.s_at
Figure 1252: PRO84390
Figure 1253: DNA327685, NP_067586.1, 208074.s_at
Figure 1254: PRO83669
Figure 1255: DNA328608, NP_006264.2, 208075.s_at
Figure 1256: PRO9932
Figure 1257: DNA255376, NP_110423.1, 208091.s_at
Figure 1258: PRO50444
Figure 1259: DNA327686, NP_005898.1, 208116.s_at
Figure 1260: PRO83670
Figure 1261A-B: DNA328609, NP_109592.1, 208121.s_at
Figure 1262: PRO84391
Figure 1263: DNA328610, NP_112601.1, 208146.s_at
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 Figure 1266: PRO37169
 Figure 1267: DNA328611, RASGRP2, 208206.s_at
 Figure 1268: PRO84393
 Figure 1269: DNA328612, NP_000166.2, 208308.s_at
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 Figure 1271: DNA270558, NP_006734.1, 208319.s_at
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 Figure 1273: DNA227614, NP_004859.1, 208336.s_at
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 Figure 1275: DNA327690, NP_004022.1, 208436.s_at
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 Figure 1278: PRO84395
 Figure 1279A-C: DNA328614, SRRM2, 208610.s_at
 Figure 1280: PRO84396
 Figure 1281A-C: DNA328615, NP_003118.1, 208611.s_at
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 Figure 1283A-C: DNA328616, NP_001448.1, 208613.s_at
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 Figure 1285: DNA326362, VAT1, 208626.s_at
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 Figure 1287: DNA325912, NP_001093.1, 208637.x_at
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 Figure 1290: PRO59579
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 Figure 1295: DNA304686, NP_002565.1, 208680.at
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 Figure 1324: PRO61321
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 Figure 1347A-B: DNA325478, NP_037534.2, 208962.s_at
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 Figure 1355: DNA328632, DJ465N24.2.1Homo, 209007.s_at
 Figure 1356: DNA328633, NP_004784.2, 209017.s_at
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Figure 2061: PRO84576
Figure 2062: DNA328843, NP_060939.1, 218099.at
Figure 2063: PRO84577
Figure 2064: DNA328844, NP_061156.1, 218111.s_at
Figure 2065: PRO82111
Figure 2066: DNA227498, NP_002125.3, 218120.s_at
Figure 2067: PRO37961
Figure 2068: DNA328845, NP_060615.1, 218126.at
Figure 2069: PRO10274
Figure 2070: DNA227264, LOC51312, 218136.s_at
Figure 2071: PRO37727
Figure 2072: DNA327857, NP_057386.1, 218142.s_at
Figure 2073: PRO83799
Figure 2074: DNA325852, NP_078813.1, 218153.at
Figure 2075: PRO82314
Figure 2076: DNA328846, NP_060522.2, 218169.at
Figure 2077: PRO84578
Figure 2078: DNA228094, NP_079416.1, 218175.at
Figure 2079: PRO38557
Figure 2080: DNA328847, NP_056338.1, 218194.at
Figure 2081: PRO84579
Figure 2082: DNA150593, NP_054747.1, 218196.at
Figure 2083: PRO12353
Figure 2084: DNA256555, NP_060042.1, 218205.s_at
Figure 2085: PRO51586
Figure 2086: DNA328848, NP_004522.1, 218212.s_at
Figure 2087: PRO84580
Figure 2088: DNA271622, NP_006020.3, 218224.at
Figure 2089: PRO59909
Figure 2090: DNA324353, NP_004538.2, 218226.s_at
Figure 2091: PRO81026
Figure 2092: DNA328849, NP_057075.1, 218232.at
Figure 2093: PRO4382
Figure 2094: DNA328850, NP_057187.1, 218254.s_at
Figure 2095: PRO84581
Figure 2096: DNA273230, NP_060914.1, 218273.s_at
Figure 2097: PRO61257
Figure 2098: DNA328851, NP_068590.1, 218276.s_at
Figure 2099: PRO84582

Figure 2100: DNA323953, NP_003507.1, 218280.x_at
 Figure 2101: PRO80685
 Figure 2102: DNA254824, AF267865, 218294.s_at
 Figure 2103: PRO49920
 Figure 2104A-B: DNA328852, NP_003609.2, 218311_at
 Figure 2105: PRO84583
 Figure 2106A-B: DNA328853, NP_065702.2, 218319_at
 Figure 2107: PRO84584
 Figure 2108: DNA328854, NP_056979.1, 218350.s_at
 Figure 2109: PRO84585
 Figure 2110: DNA328855, NP_076952.1, 218375_at
 Figure 2111: PRO9771
 Figure 2112: DNA328856, NP_068376.1, 218380_at
 Figure 2113: PRO84586
 Figure 2114: DNA328857, NP_037481.1, 218407.x_at
 Figure 2115: PRO84587
 Figure 2116: DNA324953, NP_057412.1, 218412.s_at
 Figure 2117: PRO81550
 Figure 2118A-B: DNA255062, NP_060704.1, 218424.s_at
 Figure 2119: PRO50149
 Figure 2120: DNA150661, NP_057162.1, 218446.s_at
 Figure 2121: PRO12398
 Figure 2122: DNA326218, NP_064573.1, 218447_at
 Figure 2123: PRO82631
 Figure 2124: DNA328858, HEBP1, 218450_at
 Figure 2125: PRO84588
 Figure 2126: DNA327942, NP_060596.1, 218465_at
 Figure 2127: PRO83870
 Figure 2128: DNA328859, AF154054, 218468.s_at
 Figure 2129: PRO1608
 Figure 2130A-B: DNA328860, NP_037504.1, 218469_at
 Figure 2131: PRO1608
 Figure 2132: DNA328861, NP_057030.2, 218472.s_at
 Figure 2133: PRO84589
 Figure 2134: DNA328862, NP_057626.2, 218499_at
 Figure 2135: PRO84590
 Figure 2136: DNA328863, NP_060264.1, 218503_at
 Figure 2137: PRO84591
 Figure 2138: DNA328864, NP_060726.2, 218512_at
 Figure 2139: PRO84592
 Figure 2140: DNA255432, NP_060283.1, 218516.s_at
 Figure 2141: PRO50499
 Figure 2142: DNA194326, NP_065713.1, 218538.s_at
 Figure 2143: PRO23708
 Figure 2144: DNA328865, NP_064587.1, 218557_at
 Figure 2145: PRO84593
 Figure 2146: DNA328866, NP_005691.1, 218567.x_at
 Figure 2147: PRO69644
 Figure 2148: DNA328867, NP_085053.1, 218600_at
 Figure 2149: PRO84594
 Figure 2150: DNA328868, NP_057629.1, 218611_at
 Figure 2151: PRO84595
 Figure 2152: DNA328869, NP_060892.1, 218613_at
 Figure 2153: PRO84596
 Figure 2154: DNA328870, NP_060639.1, 218614_at
 Figure 2155: PRO84597
 Figure 2156: DNA256870, NP_073600.1, 218618.s_at
 Figure 2157: PRO51800
 Figure 2158: DNA254898, NP_060840.1, 218627_at
 Figure 2159: PRO49988
 Figure 2160: DNA328871, NP_068378.1, 218631_at
 Figure 2161: PRO84598
 Figure 2162: DNA328872, NP_036528.1, 218634_at
 Figure 2163: PRO84599
 Figure 2164: DNA328873, NP_057041.1, 218698_at
 Figure 2165: PRO84600
 Figure 2166: DNA324621, NP_054754.1, 218705.s_at
 Figure 2167: PRO1285
 Figure 2168: DNA328874, NP_054778.1, 218723.s_at
 Figure 2169: PRO84601
 Figure 2170: DNA328875, NP_064554.2, 218729_at
 Figure 2171: PRO84602
 Figure 2172: DNA328876, NP_060582.1, 218772.x_at
 Figure 2173: PRO84603
 Figure 2174: DNA328877, BC020507, 218821_at
 Figure 2175: PRO84604
 Figure 2176: DNA328878, NP_060104.1, 218823.s_at
 Figure 2177: PRO84605
 Figure 2178: DNA328879, NP_064570.1, 218845_at
 Figure 2179: PRO84606
 Figure 2180: DNA227367, NP_062456.1, 218853.s_at
 Figure 2181: PRO37830
 Figure 2182: DNA327872, NP_057713.1, 218856_at
 Figure 2183: PRO83812
 Figure 2184: DNA328880, NP_060369.1, 218872_at
 Figure 2185: PRO84607
 Figure 2186: DNA328881, NP_057706.1, 218890.x_at
 Figure 2187: PRO49469
 Figure 2188: DNA287166, NP_055129.1, 218943.s_at
 Figure 2189: PRO69459
 Figure 2190: DNA328882, NP_109589.1, 218967.s_at
 Figure 2191: PRO61822
 Figure 2192: DNA327211, NP_075053.1, 218989.x_at
 Figure 2193: PRO71052
 Figure 2194: DNA255929, NP_060935.1, 218992_at
 Figure 2195: PRO50982
 Figure 2196: DNA328883, NP_037474.1, 218996_at
 Figure 2197: PRO84608
 Figure 2198: DNA227194, FLJ11000, 218999_at
 Figure 2199: PRO37657
 Figure 2200: DNA328884, NP_054884.1, 219006_at
 Figure 2201: PRO84609
 Figure 2202: DNA227187, NP_057703.1, 219014_at
 Figure 2203: PRO37650
 Figure 2204: DNA328885, NP_061108.2, 219017_at
 Figure 2205: PRO50294
 Figure 2206A-B: DNA255239, NP_004832.1, 219026.s_at

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 Figure 2208: DNA328886, NP_078811.1, 219040_at
 Figure 2209: PRO84610
 Figure 2210: DNA328887, NP_061907.1, 219045_at
 Figure 2211: PRO84611
 Figure 2212: DNA328888, NP_060436.1, 219053_s.at
 Figure 2213: PRO84612
 Figure 2214: DNA328889, NP_006005.1, 219061_s.at
 Figure 2215: PRO84613
 Figure 2216: DNA328890, NP_060403.1, 219093_at
 Figure 2217: PRO84614
 Figure 2218: DNA327877, NP_065108.1, 219099_at
 Figure 2219: PRO83816
 Figure 2220: DNA328891, NP_060263.1, 219143_s.at
 Figure 2221: PRO84615
 Figure 2222: DNA210216, NP_006860.1, 219150_s.at
 Figure 2223: PRO33752
 Figure 2224: DNA328892, NP_067643.2, 219165_at
 Figure 2225: PRO84616
 Figure 2226A-B: DNA328893, NP_065699.1, 219201_s.at
 Figure 2227: PRO9914
 Figure 2228: DNA287235, NP_060598.1, 219204_s.at
 Figure 2229: PRO69514
 Figure 2230: DNA225594, NP_037404.1, 219229_at
 Figure 2231: PRO36057
 Figure 2232: DNA328894, NP_060796.1, 219243_at
 Figure 2233: PRO84617
 Figure 2234: DNA328895, NP_071762.2, 219259_at
 Figure 2235: PRO1317
 Figure 2236: DNA328896, NP_079037.1, 219265_at
 Figure 2237: PRO84618
 Figure 2238: DNA328897, TRPV2, 219282_s.at
 Figure 2239: PRO12382
 Figure 2240: DNA273489, NP_055210.1, 219290_x.at
 Figure 2241: PRO61472
 Figure 2242A-B: DNA328898, NP_060261.1, 219316_s.at
 Figure 2243: PRO84619
 Figure 2244: DNA328899, NP_061024.1, 219326_s.at
 Figure 2245: PRO84620
 Figure 2246A-B: DNA255889, NP_061764.1, 219340_s.at
 Figure 2247: PRO50942
 Figure 2248: DNA328900, NP_060814.1, 219344_at
 Figure 2249: PRO84621
 Figure 2250: DNA254518, NP_057354.1, 219371_s.at
 Figure 2251: PRO49625
 Figure 2252: DNA188342, NP_064510.1, 219385_at
 Figure 2253: PRO21718
 Figure 2254: DNA256417, NP_077271.1, 219402_s.at
 Figure 2255: PRO51457
 Figure 2256A-B: DNA327887, NP_006656.1, 219403_s.at
 Figure 2257: PRO83823
 Figure 2258: DNA327888, NP_071732.1, 219412_at
 Figure 2259: PRO83824
 Figure 2260: DNA328901, FLJ20533, 219449_s.at
 Figure 2261: PRO84622
 Figure 2262: DNA328902, NP_071750.1, 219452_at
 Figure 2263: PRO84623
 Figure 2264: DNA328903, NP_002805.1, 219485_s.at
 Figure 2265: PRO84624
 Figure 2266: DNA328904, NP_076941.1, 219491_at
 Figure 2267: PRO84625
 Figure 2268A-B: DNA328905, NP_075392.1, 219496_at
 Figure 2269: PRO84626
 Figure 2270: DNA328906, NP_078855.1, 219506_at
 Figure 2271: PRO84627
 Figure 2272: DNA328907, NP_000067.1, 219534_x.at
 Figure 2273: PRO84628
 Figure 2274: DNA328908, 7691567.2, 219540_at
 Figure 2275: PRO84629
 Figure 2276: DNA225636, NP_065696.1, 219557_s.at
 Figure 2277: PRO36099
 Figure 2278A-B: DNA328909, NP_078800.2, 219558_at
 Figure 2279: PRO84630
 Figure 2280: DNA328910, NP_057666.1, 219593_at
 Figure 2281: PRO38848
 Figure 2282: DNA328911, MS4A4A, 219607_s.at
 Figure 2283: PRO84631
 Figure 2284: DNA328912, NP_060287.1, 219622_at
 Figure 2285: PRO84632
 Figure 2286: DNA328913, NP_079213.1, 219631_at
 Figure 2287: PRO84633
 Figure 2288: DNA328914, NP_060883.1, 219634_at
 Figure 2289: PRO36664
 Figure 2290: DNA327892, NP_060470.1, 219648_at
 Figure 2291: PRO83828
 Figure 2292: DNA328915, NP_055056.2, 219654_at
 Figure 2293: PRO84634
 Figure 2294: DNA228002, NP_071744.1, 219666_at
 Figure 2295: PRO38465
 Figure 2296: DNA328916, NP_071932.1, 219678_x.at
 Figure 2297: PRO84635
 Figure 2298: DNA287206, NP_060124.1, 219691_at
 Figure 2299: PRO69488
 Figure 2300: DNA328917, NP_061838.1, 219725_at
 Figure 2301: PRO7306
 Figure 2302: DNA328918, NP_078935.1, 219770_at
 Figure 2303: PRO84636
 Figure 2304: DNA328919, NP_078987.1, 219777_at
 Figure 2305: PRO84637
 Figure 2306: DNA227152, NP_038467.1, 219788_at
 Figure 2307: PRO37615
 Figure 2308: DNA328920, NP_061129.1, 219837_s.at
 Figure 2309: PRO4425
 Figure 2310: DNA256033, NP_060164.1, 219858_s.at
 Figure 2311: PRO51081
 Figure 2312: DNA254838, NP_078904.1, 219874_at

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 Figure 2314: DNA328921, NP_057079.1, 219878.s_at
 Figure 2315: PRO84638
 Figure 2316: DNA256325, NP_005470.1, 219889_at
 Figure 2317: PRO51367
 Figure 2318: DNA328922, NP_037384.1, 219890_at
 Figure 2319: PRO84639
 Figure 2320: DNA328923, NP_075379.1, 219892_at
 Figure 2321: PRO84640
 Figure 2322: DNA256608, NP_060408.1, 219895_at
 Figure 2323: PRO51611
 Figure 2324: DNA328924, NP_057150.2, 219933_at
 Figure 2325: PRO84641
 Figure 2326: DNA255456, NP_057268.1, 219947_at
 Figure 2327: PRO50523
 Figure 2328: DNA227804, NP_065394.1, 219952.s_at
 Figure 2329: PRO38267
 Figure 2330: DNA328925, NP_076403.1, 220005_at
 Figure 2331: PRO84642
 Figure 2332: DNA256467, NP_079054.1, 220009_at
 Figure 2333: PRO51504
 Figure 2334A-B: DNA292946, NP_061160.1, 220023_at
 Figure 2335: PRO70613
 Figure 2336: DNA171414, NP_009130.1, 220034_at
 Figure 2337: PRO20142
 Figure 2338: DNA328926, NP_064703.1, 220046.s_at
 Figure 2339: PRO84643
 Figure 2340A-B: DNA221079, NP_071445.1, 220066_at
 Figure 2341: PRO34753
 Figure 2342: DNA256091, NP_071385.1, 220094.s_at
 Figure 2343: PRO51141
 Figure 2344: DNA328927, NP_078993.2, 220122_at
 Figure 2345: PRO84644
 Figure 2346: DNA328928, NP_068377.1, 220178_at
 Figure 2347: PRO84645
 Figure 2348: DNA324716, NP_463459.1, 220189.s_at
 Figure 2349: PRO81347
 Figure 2350: DNA228059, NP_073742.1, 220199.s_at
 Figure 2351: PRO38522
 Figure 2352: DNA328929, NP_060375.1, 220240.s_at
 Figure 2353: PRO84646
 Figure 2354A-B: DNA328930, NP_038465.1, 220253.s_at
 Figure 2355: PRO23525
 Figure 2356: DNA328931, NP_004226.1, 220266.s_at
 Figure 2357: PRO84647
 Figure 2358: DNA328932, NP_079057.1, 220301_at
 Figure 2359: PRO84648
 Figure 2360: DNA328933, NP_057466.1, 220307_at
 Figure 2361: PRO9891
 Figure 2362: DNA256735, NP_060175.1, 220333_at
 Figure 2363: PRO51669
 Figure 2364A-B: DNA328934, EML4, 220386.s_at
 Figure 2365: PRO84649
 Figure 2366: DNA328935, NP_009002.1, 220387.s_at
 Figure 2367: PRO84650
 Figure 2368: DNA254861, MCOLN3, 220484_at
 Figure 2369: PRO49953
 Figure 2370: DNA328936, NP_066998.1, 220491_at
 Figure 2371: PRO1003
 Figure 2372: DNA328937, PHEMX, 220558.x_at
 Figure 2373: PRO12380
 Figure 2374: DNA328938, NP_060617.1, 220643.s_at
 Figure 2375: PRO84651
 Figure 2376: DNA323756, NP_057267.2, 220688.s_at
 Figure 2377: PRO80512
 Figure 2378: DNA328939, NP_008834.1, 220741.s_at
 Figure 2379: PRO84652
 Figure 2380: DNA288247, NP_478059.1, 220892.s_at
 Figure 2381: PRO70011
 Figure 2382: DNA328940, NP_078893.1, 220933.s_at
 Figure 2383: PRO84653
 Figure 2384: DNA328941, NP_055218.2, 220937.s_at
 Figure 2385: PRO84654
 Figure 2386: DNA327953, NP_055182.2, 220942.x_at
 Figure 2387: PRO83878
 Figure 2388A-B: DNA323882, NP_000692.2, 220948.s_at
 Figure 2389: PRO80625
 Figure 2390: DNA327917, NP_112240.1, 220966.x_at
 Figure 2391: PRO83852
 Figure 2392: DNA328942, NP_112216.2, 220985.s_at
 Figure 2393: PRO84655
 Figure 2394: DNA328943, NP_036566.1, 221041.s_at
 Figure 2395: PRO51680
 Figure 2396: DNA328944, NP_060554.1, 221078.s_at
 Figure 2397: PRO84656
 Figure 2398: DNA328945, NP_079177.2, 221081.s_at
 Figure 2399: PRO84657
 Figure 2400: DNA328946, NP_055164.1, 221087.s_at
 Figure 2401: PRO12343
 Figure 2402: DNA328947, NP_055245.1, 221188.s_at
 Figure 2403: PRO84658
 Figure 2404: DNA257293, NP_110396.1, 221210.s_at
 Figure 2405: PRO51888
 Figure 2406: DNA327920, NP_110431.1, 221245.s_at
 Figure 2407: PRO83855
 Figure 2408A-C: DNA328287, NP_072174.2, 221246.x_at
 Figure 2409: PRO84163
 Figure 2410: DNA328948, NP_110437.1, 221253.s_at
 Figure 2411: PRO84659
 Figure 2412: DNA256432, NP_110415.1, 221266.s_at
 Figure 2413: PRO51471
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 Figure 2418: DNA328949, AF157510, 221487.s_at

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 Figure 2420: DNA328950, NP_057025.1, 221504.s_at
 Figure 2421: PRO84661
 Figure 2422A-B: DNA328951, HSM802232, 221523.s_at
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 Figure 2424: DNA328952, NP_067067.1, 221524.s_at
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 Figure 2426A-B: DNA273901, NP_110389.1, 221530.s_at
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 Figure 2428: DNA274676, DKFZp564A176Homo, 221538.s_at
 Figure 2429: DNA328953, NP_004086.1, 221539.at
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 Figure 2431A-B: DNA328954, NP_113664.1, 221541.at
 Figure 2432: PRO9851
 Figure 2433A-B: DNA269992, HUMACYLCOA, 221561.at
 Figure 2434: PRO58388
 Figure 2435: DNA328955, NP_054887.1, 221570.s_at
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 Figure 2437A-B: DNA328956, AF110908, 221571.at
 Figure 2438: DNA188321, NP_004855.1, 221577.x_at
 Figure 2439: PRO21896
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 Figure 2441: PRO23859
 Figure 2442: DNA328958, BC001663, 221593.s_at
 Figure 2443: PRO84665
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 Figure 2445: PRO4302
 Figure 2446: DNA254777, NP_055140.1, 221676.s_at
 Figure 2447: PRO49875
 Figure 2448: DNA327526, NP_065727.2, 221679.s_at
 Figure 2449: PRO83574
 Figure 2450: DNA328960, NP_076426.1, 221692.s_at
 Figure 2451: PRO84666
 Figure 2452: DNA327929, AK001785, 221748.s_at
 Figure 2453: PRO83861
 Figure 2454: DNA328961, NP_443112.1, 221756.at
 Figure 2455: PRO84667
 Figure 2456: DNA328962, BC021574, 221759.at
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 Figure 2461: PRO83862
 Figure 2462: DNA328964, AK056028, 221770.at
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 Figure 2465A-B: DNA328966, BAB14908.1, 221790.s_at
 Figure 2466: PRO84670
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 Figure 2469: DNA274058, NP_057203.1, 221816.s_at
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 Figure 2496: DNA287209, NP_056350.1, 222154.s_at
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 Figure 2499: PRO47688
 Figure 2500: DNA328976, BC019091, 222206.s_at
 Figure 2501: PRO84677
 Figure 2502: DNA256784, NP_075069.1, 222209.s_at
 Figure 2503: PRO51716
 Figure 2504: DNA328977, NP_071344.1, 222216.s_at
 Figure 2505: PRO84678
 Figure 2506: DNA328978, NP_060373.1, 222244.s_at
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 Figure 2512: DNA328981, AF443871, 222294.s_at
 Figure 2513: PRO24633
 Figure 2514: DNA328982, 154391.1, 222313.at
 Figure 2515: PRO84682
 Figure 2516: DNA328983, 206335.1, 222366.at
 Figure 2517: PRO84683

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTSI. Definitions

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "PRO polypeptide" refers to each individual PRO/number polypeptide disclosed herein. All disclosures in this specification which refer to the "PRO polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "PRO polypeptide" also includes variants of the PRO/number polypeptides disclosed herein.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., Prot. Eng. 10:1-6 (1997) and von Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20 amino acids in length, alternatively at least about 30 amino acids in length, alternatively at least about 40 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 60 amino acids in length, alternatively at least about 70 amino acids in length, alternatively at least about 80 amino acids in length, alternatively at least about 90 amino acids in length, alternatively at least about 100 amino acids in length,

alternatively at least about 150 amino acids in length, alternatively at least about 200 amino acids in length, alternatively at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO", wherein "PRO" represents the amino acid sequence of a hypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, and "X", "Y" and "Z" each represent different hypothetical amino acid residues.

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

However, % amino acid sequence identity values may also be obtained as described below by using the WU-

BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (i.e., the sequence against which the PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest. For example, in the statement "a polypeptide comprising an the amino acid sequence A which has or having at least 80% amino acid sequence identity to the amino acid sequence B", the amino acid sequence A is the comparison amino acid sequence of interest and the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about 80% nucleic acid

sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 210 nucleotides in length, alternatively at least about 240 nucleotides in length, alternatively at least about 270 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 900 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity" with respect to PRO-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence

D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA", wherein "PRO-DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides.

Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % nucleic acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (i.e., the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement "an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

5

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO polypeptide as disclosed herein. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" PRO polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the specific polypeptide-encoding nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-PRO monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-PRO antibody compositions with polypeptidic specificity, single chain anti-PRO antibodies, and fragments of anti-PRO antibodies (see below). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a

solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

"Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native PRO polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native PRO polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for identifying agonists or antagonists of a PRO polypeptide may comprise contacting a PRO polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the PRO polypeptide.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those

in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time.

5 "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

10 Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of
15 physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating
20 agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEENTM, polyethylene glycol (PEG), and PLURONICSTM.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain
25 antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

30 "Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising
35 only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge
40 region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains

bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

"Single-chain Fv" or "sFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass

(e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No.

4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a PRO polypeptide or antibody thereto) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.

The term "immune related disease" means a disease in which a component of the immune system of a mammal causes, mediates or otherwise contributes to a morbidity in the mammal. Also included are diseases in which stimulation or intervention of the immune response has an ameliorative effect on progression of the disease. Included within this term are immune-mediated inflammatory diseases, non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, *etc.*

The term "monocyte/macrophage mediated disease" means a disease in which monocytes/macrophages directly or indirectly mediate or otherwise contribute to a morbidity in a mammal. The monocyte/macrophage mediated disease may be associated with cell mediated effects, lymphokine mediated effects, *etc.*, and even effects associated with other immune cells if the cells are stimulated, for example, by the lymphokines secreted by monocytes/macrophages.

Examples of immune-related and inflammatory diseases, some of which are immune mediated, which can be treated according to the invention include systemic lupus erythematosus, rheumatoid arthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis (scleroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis), diabetes mellitus, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis), demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease (ulcerative colitis: Crohn's disease), gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft -versus-host-disease. Infectious diseases including viral diseases such as AIDS (HIV infection), hepatitis A, B, C, D, and E, herpes, *etc.*, bacterial infections, fungal infections, protozoal infections and parasitic infections.

The term "effective amount" is a concentration or amount of a PRO polypeptide and/or agonist/antagonist which results in achieving a particular stated purpose. An "effective amount" of a PRO polypeptide or agonist or antagonist thereof may be determined empirically. Furthermore, a "therapeutically effective amount" is a concentration or amount of a PRO polypeptide and/or agonist/antagonist which is effective for achieving a stated therapeutic effect. This amount may also be determined empirically.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (*e.g.*, I^{131} , I^{125} , Y^{90} and Re^{186}), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include adriamycin, doxorubicin, epirubicin, 5-fluorouracil, cytosine arabinoside ("Ara-C"), cyclophosphamide, thiotepa, busulfan, cytoxin, taxoids, *e.g.*, paclitaxel (Taxol, Bristol-Myers Squibb Oncology, Princeton, NJ), and doxetaxel (Taxotere, Rhône-Poulenc Rorer, Antony, France), toxotere, methotrexate, cisplatin, melphalan, vinblastine, bleomycin, etoposide, ifosfamide, mitomycin C, mitoxantrone, vincristine, vinorelbine, carboplatin, teniposide, daunomycin, carminomycin, aminopterin, dactinomycin, mitomycins, esperamicins (see U.S. Pat. No. 4,675,187), melphalan and other related nitrogen mustards. Also included in this definition are hormonal agents that act to regulate or inhibit hormone action on tumors such as tamoxifen and onapristone.

A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially cancer cell overexpressing any of the genes identified herein, either *in vitro* or *in vivo*. Thus, the growth inhibitory agent is one which significantly reduces the percentage of cells overexpressing such genes in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxol, and topo II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in *The Molecular Basis of Cancer*, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogens, and antineoplastic drugs" by Murakami *et al.* (WB Saunders: Philadelphia, 1995), especially p. 13.

The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- α and - β ; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- β ; platelet-growth factor; transforming growth factors (TGFs) such as TGF- α and TGF- β ; insulin-like growth factor-I and -II; erythropoietin (EPO);

osteoinductive factors; interferons such as interferon- α , - β , and - γ ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1 α , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF- α or TNF- β ; and other polypeptide factors including LIF and kit ligand (KL).

5 As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the
10 desired binding specificity which is other than the antigen recognition and binding site of an antibody (*i.e.*, is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any
15 immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

Table 1

```

/*
5  *
  * C-C increased from 12 to 15
  * Z is average of EQ
  * B is average of ND
  * match with stop is _M; stop-stop = 0; J (joker) match = 0
10 */
#define _M      -8      /* value of a match with a stop */

int _day[26][26] = {
/*  A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
15 /* A */ { 2, 0,-2, 0, 0,-4, 1,-1,-1, 0,-1,-2,-1, 0, _M, 1, 0,-2, 1, 1, 0, 0,-6, 0,-3, 0},
/* B */ { 0, 3,-4, 3, 2,-5, 0, 1,-2, 0, 0,-3,-2, 2, _M,-1, 1, 0, 0, 0, 0,-2,-5, 0,-3, 1},
/* C */ {-2,-4,15,-5,-5,-4,-3,-3,-2, 0,-5,-6,-5,-4, _M,-3,-5,-4, 0,-2, 0,-2,-8, 0, 0,-5},
/* D */ { 0, 3,-5, 4, 3,-6, 1, 1,-2, 0, 0,-4,-3, 2, _M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 2},
/* E */ { 0, 2,-5, 3, 4,-5, 0, 1,-2, 0, 0,-3,-2, 1, _M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 3},
20 /* F */ {-4,-5,-4,-6,-5, 9,-5,-2, 1, 0,-5, 2, 0,-4, _M,-5,-5,-4,-3,-3, 0,-1, 0, 0, 7,-5},
/* G */ { 1, 0,-3, 1, 0,-5, 5,-2,-3, 0,-2,-4,-3, 0, _M,-1,-1,-3, 1, 0, 0,-1,-7, 0,-5, 0},
/* H */ {-1, 1,-3, 1, 1,-2,-2, 6,-2, 0, 0,-2,-2, 2, _M, 0, 3, 2,-1,-1, 0,-2,-3, 0, 0, 2},
/* I */ {-1,-2,-2,-2,-2, 1,-3,-2, 5, 0,-2, 2, 2,-2, _M,-2,-2,-2,-1, 0, 0, 4,-5, 0,-1,-2},
/* J */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
25 /* K */ {-1, 0,-5, 0, 0,-5,-2, 0,-2, 0, 5,-3, 0, 1, _M,-1, 1, 3, 0, 0, 0,-2,-3, 0,-4, 0},
/* L */ {-2,-3,-6,-4,-3, 2,-4,-2, 2, 0,-3, 6, 4,-3, _M,-3,-2,-3,-3,-1, 0, 2,-2, 0,-1,-2},
/* M */ {-1,-2,-5,-3,-2, 0,-3,-2, 2, 0, 0, 4, 6,-2, _M,-2,-1, 0,-2,-1, 0, 2,-4, 0,-2,-1},
/* N */ { 0, 2,-4, 2, 1,-4, 0, 2,-2, 0, 1,-3,-2, 2, _M,-1, 1, 0, 1, 0, 0,-2,-4, 0,-2, 1},
/* O */ { _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M},
30 0, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M},
/* P */ { 1,-1,-3,-1,-1,-5,-1, 0,-2, 0,-1,-3,-2,-1, _M, 6, 0, 0, 1, 0, 0,-1,-6, 0,-5, 0},
/* Q */ { 0, 1,-5, 2, 2,-5,-1, 3,-2, 0, 1,-2,-1, 1, _M, 0, 4, 1,-1,-1, 0,-2,-5, 0,-4, 3},
/* R */ {-2, 0,-4,-1,-1,-4,-3, 2,-2, 0, 3,-3, 0, 0, _M, 0, 1, 6, 0,-1, 0,-2, 2, 0,-4, 0},
/* S */ { 1, 0, 0, 0, 0,-3, 1,-1,-1, 0, 0,-3,-2, 1, _M, 1,-1, 0, 2, 1, 0,-1,-2, 0,-3, 0},
35 /* T */ { 1, 0,-2, 0, 0,-3, 0,-1, 0, 0, 0,-1,-1, 0, _M, 0,-1,-1, 1, 3, 0, 0,-5, 0,-3, 0},
/* U */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */ { 0,-2,-2,-2,-2,-1,-1,-2, 4, 0,-2, 2, 2,-2, _M,-1,-2,-2,-1, 0, 0, 4,-6, 0,-2,-2},
/* W */ {-6,-5,-8,-7,-7, 0,-7,-3,-5, 0,-3,-2,-4,-4, _M,-6,-5, 2,-2,-5, 0,-6,17, 0, 0,-6},
/* X */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
40 /* Y */ {-3,-3, 0,-4,-4, 7,-5, 0,-1, 0,-4,-1,-2,-2, _M,-5,-4,-4,-3,-3, 0,-2, 0, 0,10,-4},
/* Z */ { 0, 1,-5, 2, 3,-5, 0, 2,-2, 0, 0,-2,-1, 1, _M, 0, 3, 0, 0, 0, 0,-2,-6, 0,-4, 4}
};

```

Table 1 (cont')

```

/*
*/
#include <stdio.h>
5  #include <ctype.h>

#define MAXJMP      16      /* max jumps in a diag */
#define MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define JMPS        1024    /* max jmps in an path */
10  #define MX        4      /* save if there's at least MX-1 bases since last jmp */

#define DMAT        3      /* value of matching bases */
#define DMIS        0      /* penalty for mismatched bases */
#define DINS0       8      /* penalty for a gap */
15  #define DINS1     1      /* penalty per base */
#define PINS0       8      /* penalty for a gap */
#define PINS1       4      /* penalty per residue */

struct jmp {
20      short         n[MAXJMP];    /* size of jmp (neg for del) */
      unsigned short x[MAXJMP];    /* base no. of jmp in seq x */
};                                  /* limits seq to 2^16 -1 */

struct diag {
25      int           score;        /* score at last jmp */
      long           offset;       /* offset of prev block */
      short          ijmp;         /* current jmp index */
      struct jmp      jp;          /* list of jmps */
};

30  struct path {
      int            spc;           /* number of leading spaces */
      short          n[JMPS];      /* size of jmp (gap) */
      int            x[JMPS];      /* loc of jmp (last elem before gap) */
35  };

char      *ofile;                  /* output file name */
char      *namex[2];               /* seq names: getseqs() */
char      *prog;                   /* prog name for err msgs */
40  char      *seqx[2];             /* seqs: getseqs() */
int        dmax;                   /* best diag: nw() */
int        dmax0;                  /* final diag */
int        dna;                    /* set if dna: main() */
int        endgaps;                /* set if penalizing end gaps */
45  int        gapx, gapy;           /* total gaps in seqs */
int        len0, len1;             /* seq lens */
int        ngapx, ngapy;           /* total size of gaps */
int        smax;                   /* max score: nw() */
int        *xbm;                   /* bitmap for matching */
50  long       offset;              /* current offset in jmp file */
struct     diag      *dx;          /* holds diagonals */
struct     path      pp[2];        /* holds path for seqs */

char      *calloc(), *malloc(), *index(), *strcpy();
55  char      *getseq(), *g_calloc();

```

60

Table 1 (cont')

```

/* Needleman-Wunsch alignment program
*
* usage: progs file1 file2
5  * where file1 and file2 are two dna or two protein sequences.
* The sequences can be in upper- or lower-case and may contain ambiguity
* Any lines beginning with ';', '>' or '<' are ignored
* Max file length is 65535 (limited by unsigned short x in the jmp struct)
* A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
10 * Output is in the file "align.out"
*
* The program may create a tmp file in /tmp to hold info about traceback.
* Original version developed under BSD 4.3 on a vax 8650
*/
15 #include "nw.h"
#include "day.h"

static _dbval[26] = {
20 1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static _pbval[26] = {
25 1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
128, 256, 0xFFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)
30     main
    int      ac;
    char     *av[ ];
{
    prog = av[0];
35     if (ac != 3) {
        fprintf(stderr, "usage: %s file1 file2\n", prog);
        fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
        fprintf(stderr, "The sequences can be in upper- or lower-case\n");
        fprintf(stderr, "Any lines beginning with ';' or '<' are ignored\n");
40         fprintf(stderr, "Output is in the file \"align.out\"\n");
        exit(1);
    }
    namex[0] = av[1];
    namex[1] = av[2];
45     seqx[0] = getseq(namex[0], &len0);
    seqx[1] = getseq(namex[1], &len1);
    xbm = (dna)? _dbval : _pbval;

    endgaps = 0;                                /* 1 to penalize endgaps */
50     ofile = "align.out";                      /* output file */

    nw();                                       /* fill in the matrix, get the possible jumps */
    readjumps();                             /* get the actual jumps */
    print();                                  /* print stats, alignment */
55     cleanup(0);                             /* unlink any tmp files */
}
60

```

Table 1 (cont')

```

/* do the alignment, return best score: main()
* dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
* pro: PAM 250 values
5  * When scores are equal, we prefer mismatches to any gap, prefer
* a new gap to extending an ongoing gap, and prefer a gap in seqx
* to a gap in seq y.
*/
nw()
10  {
    char      *px, *py;          /* seqs and ptrs */
    int        *ndely, *dely;     /* keep track of dely */
    int        ndelx, delx;       /* keep track of delx */
15  int        *tmp;             /* for swapping row0, row1 */
    int        mis;              /* score for each type */
    int        ins0, ins1;        /* insertion penalties */
    register   id;               /* diagonal index */
    register   ij;               /* jmp index */
20  register   *col0, *col1;      /* score for curr, last row */
    register   xx, yy;           /* index into seqs */

    dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

25  ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
    dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
    col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
    col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
    ins0 = (dna)? DINS0 : PINS0;
30  ins1 = (dna)? DINS1 : PINS1;

    smax = -10000;
    if (endgaps) {
        for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
35  col0[yy] = dely[yy] = col0[yy-1] - ins1;
            ndely[yy] = yy;
        }
        col0[0] = 0;          /* Waterman Bull Math Biol 84 */
    }
40  else
        for (yy = 1; yy <= len1; yy++)
            dely[yy] = -ins0;

    /* fill in match matrix
45  */
    for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
        /* initialize first entry in col
        */
        if (endgaps) {
50  if (xx == 1)
            col1[0] = delx = -(ins0+ins1);
            else
            col1[0] = delx = col0[0] - ins1;
            ndelx = xx;
55  }
        else {
            col1[0] = 0;
            delx = -ins0;
            ndelx = 0;
60  }
    }

```

Table 1 (cont')

...nw

```

5      for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
        mis = col0[yy-1];
        if (dna)
            mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
        else
            mis += _day[*px-'A'][*py-'A'];

10      /* update penalty for del in x seq;
        * favor new del over ongong del
        * ignore MAXGAP if weighting endgaps
        */
        if (endgaps || ndely[yy] < MAXGAP) {
15            if (col0[yy] - ins0 >= dely[yy]) {
                dely[yy] = col0[yy] - (ins0+ins1);
                ndely[yy] = 1;
            } else {
                dely[yy] -= ins1;
                ndely[yy]++;
            }
        } else {
20            if (col0[yy] - (ins0+ins1) >= dely[yy]) {
                dely[yy] = col0[yy] - (ins0+ins1);
                ndely[yy] = 1;
            } else
25                ndely[yy]++;
        }

30      /* update penalty for del in y seq;
        * favor new del over ongong del
        */
        if (endgaps || ndelx < MAXGAP) {
            if (col1[yy-1] - ins0 >= delx) {
35                delx = col1[yy-1] - (ins0+ins1);
                ndelx = 1;
            } else {
                delx -= ins1;
                ndelx++;
            }
40        } else {
            if (col1[yy-1] - (ins0+ins1) >= delx) {
                delx = col1[yy-1] - (ins0+ins1);
                ndelx = 1;
            } else
45                ndelx++;
        }

50      /* pick the maximum score; we're favoring
        * mis over any del and delx over dely
        */

```

55

60

Table 1 (cont')

...nw

```

id = xx - yy + len1 - 1;
if (mis >= delx && mis >= dely[yy])
5     col1[yy] = mis;
else if (delx >= dely[yy]) {
    col1[yy] = delx;
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
10     && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
            writejumps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
        }
    }
    dx[id].jp.n[ij] = ndelx;
    dx[id].jp.x[ij] = xx;
    dx[id].score = delx;
}
else {
25     col1[yy] = dely[yy];
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
        && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
30             writejumps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
        }
    }
    dx[id].jp.n[ij] = -ndely[yy];
    dx[id].jp.x[ij] = xx;
    dx[id].score = dely[yy];
}
40     if (xx == len0 && yy < len1) {
        /* last col
        */
        if (endgaps)
            col1[yy] -= ins0+ins1*(len1-yy);
        if (col1[yy] > smax) {
45             smax = col1[yy];
            dmax = id;
        }
    }
}
50     if (endgaps && xx < len0)
        col1[yy-1] -= ins0+ins1*(len0-xx);
    if (col1[yy-1] > smax) {
        smax = col1[yy-1];
55         dmax = id;
    }
}
tmp = col0; col0 = col1; col1 = tmp;
}
(void) free((char *)ndely);
(void) free((char *)dely);
(void) free((char *)col0);
(void) free((char *)col1);
}

```

Table 1 (cont')

```

/*
*
* print() -- only routine visible outside this module
5  *
* static:
* getmat() -- trace back best path, count matches: print()
* pr_align() -- print alignment of described in array p[ ]: print()
* dumpblock() -- dump a block of lines with numbers, stars: pr_align()
10 * nums() -- put out a number line: dumpblock()
* putline() -- put out a line (name, [num], seq, [num]): dumpblock()
* stars() -- put a line of stars: dumpblock()
* stripname() -- strip any path and prefix from a seqname
*/
15
#include "nw.h"

#define SPC      3
#define P_LINE   256      /* maximum output line */
20 #define P_SPC   3        /* space between name or num and seq */

extern _day[26][26];
int olen;                /* set output line length */
FILE *fx;                /* output file */
25

print()
{
    int lx, ly, firstgap, lastgap;      /* overlap */
30
    if ((fx = fopen(ofile, "w")) == 0) {
        fprintf(stderr, "%s: can't write %s\n", prog, ofile);
        cleanup(1);
    }
35
    fprintf(fx, "< first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "< second sequence: %s (length = %d)\n", namex[1], len1);
    olen = 60;
    lx = len0;
    ly = len1;
40
    firstgap = lastgap = 0;
    if (dmax < len1 - 1) { /* leading gap in x */
        pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
45
    else if (dmax > len1 - 1) { /* leading gap in y */
        pp[1].spc = firstgap = dmax - (len1 - 1);
        lx -= pp[1].spc;
    }
    if (dmax0 < len0 - 1) { /* trailing gap in x */
50
        lastgap = len0 - dmax0 - 1;
        lx -= lastgap;
    }
    else if (dmax0 > len0 - 1) { /* trailing gap in y */
55
        lastgap = dmax0 - (len0 - 1);
        ly -= lastgap;
    }
    getmat(lx, ly, firstgap, lastgap);
    pr_align();
}
60

```

Table 1 (cont')

```

/*
 * trace back the best path, count matches
 */
5  static
   getmat(lx, ly, firstgap, lastgap)                                getmat
       int      lx, ly;                                           /* "core" (minus endgaps) */
       int      firstgap, lastgap;                                /* leading trailing overlap */
   {
10      int      nm, i0, i1, siz0, siz1;
       char      outx[32];
       double     pct;
       register   n0, n1;
15      register char  *p0, *p1;

       /* get total matches, score
        */
       i0 = i1 = siz0 = siz1 = 0;
       p0 = seqx[0] + pp[1].spc;
20      p1 = seqx[1] + pp[0].spc;
       n0 = pp[1].spc + 1;
       n1 = pp[0].spc + 1;

       nm = 0;
25      while ( *p0 && *p1 ) {
           if (siz0) {
               p1++;
               n1++;
               siz0--;
30           }
           else if (siz1) {
               p0++;
               n0++;
               siz1--;
35           }
           else {
               if (xbm[*p0-'A']&xbm[*p1-'A'])
                   nm++;
               if (n0++ == pp[0].x[i0])
                   siz0 = pp[0].n[i0++];
40               if (n1++ == pp[1].x[i1])
                   siz1 = pp[1].n[i1++];
               p0++;
               p1++;
45           }
       }

       /* pct homology:
        * if penalizing endgaps, base is the shorter seq
50      * else, knock off overhangs and take shorter core
        */
       if (endgaps)
           lx = (len0 < len1)? len0 : len1;
       else
55          lx = (lx < ly)? lx : ly;
       pct = 100.*(double)nm/(double)lx;
       fprintf(fx, "\n");
       fprintf(fx, "< %d match%s in an overlap of %d: %.2f percent similarity\n",
60          nm, (nm == 1)? "" : "es", lx, pct);

```

Table 1 (cont')

```

fprintf(fx, "< gaps in first sequence: %d", gapx);
...getmat
5  if (gapx) {
    (void) sprintf(outx, " (%d %s%s)",
        ngapx, (dna)? "base":"residue", (ngapx == 1)? "" : "s");
    fprintf(fx, "%s", outx);

10  fprintf(fx, ", gaps in second sequence: %d", gapy);
    if (gapy) {
        (void) sprintf(outx, " (%d %s%s)",
            ngapy, (dna)? "base":"residue", (ngapy == 1)? "" : "s");
        fprintf(fx, "%s", outx);

15  }
    if (dna)
        fprintf(fx,
            "\n< score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
            smax, DMAT, DMIS, DINS0, DINS1);

20  else
        fprintf(fx,
            "\n< score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
            smax, PINS0, PINS1);
    if (endgaps)
25  fprintf(fx,
        "< endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
        firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
        lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
    else
30  fprintf(fx, "< endgaps not penalized\n");
}

static nm;          /* matches in core -- for checking */
static lmax;        /* lengths of stripped file names */
static ij[2];       /* jmp index for a path */
35 static nc[2];      /* number at start of current line */
static ni[2];       /* current elem number -- for gapping */
static siz[2];
static char *ps[2];  /* ptr to current element */
static char *po[2];  /* ptr to next output char slot */
40 static char out[2][P_LINE]; /* output line */
static char star[P_LINE]; /* set by stars() */

/*
 * print alignment of described in struct path pp[ ]
 */
45 static
pr_align()
{
    pr_align

50  {
    int nn;          /* char count */
    int more;
    register i;

    for (i = 0, lmax = 0; i < 2; i++) {
55  nn = stripname(name[i]);
    if (nn > lmax)
        lmax = nn;

    nc[i] = 1;
    ni[i] = 1;
    siz[i] = ij[i] = 0;
    ps[i] = seqx[i];
    po[i] = out[i];
60
    }

```

Table 1 (cont')

```

for (nn = nm = 0, more = 1; more; ) {
...pr_align
    for (i = more = 0; i < 2; i++) {
5         /*
           * do we have more of this sequence?
           */
           if (!*ps[i])
10                continue;

           more++;

           if (pp[i].spc) { /* leading space */
               *po[i]++ = ' ';
               pp[i].spc--;
15           }
           else if (siz[i]) { /* in a gap */
               *po[i]++ = '-';
               siz[i]--;
20           }
           else { /* we're putting a seq element
                  */
               *po[i] = *ps[i];
               if (islower(*ps[i]))
25                   *ps[i] = toupper(*ps[i]);
               po[i]++;
               ps[i]++;

               /*
30                  * are we at next gap for this seq?
                  */
               if (ni[i] == pp[i].x[ij[i]]) {
                   /*
35                  * we need to merge all gaps
                   * at this location
                   */
                   siz[i] = pp[i].n[ij[i] + +];
                   while (ni[i] == pp[i].x[ij[i]])
                       siz[i] += pp[i].n[ij[i] + +];
40                   }
                   ni[i]++;
               }
           }
           if (++nm == olen || !more && nn) {
45               dumpblock();
               for (i = 0; i < 2; i++)
                   po[i] = out[i];
               nn = 0;
           }
50     }
}

/*
 * dump a block of lines, including numbers, stars: pr_align()
55 */
static
dumpblock()
{
    dumpblock

60 {
    register i;
    for (i = 0; i < 2; i++)
        *po[i]-- = '\0';
}

```

Table 1 (cont')**...dumpblock**

```

5      (void) putc('\n', fx);
      for (i = 0; i < 2; i++) {
          if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
              if (i == 0)
                  nums(i);
              if (i == 0 && *out[1])
10                 stars();
              putline(i);
              if (i == 0 && *out[1])
                  fprintf(fx, star);
              if (i == 1)
15                 nums(i);
          }
      }
  }

20  /*
   * put out a number line: dumpblock()
   */
   static
   nums(ix)
25  {
      int      ix;      /* index in out[ ] holding seq line */

      char      nline[P_LINE];
      register  i, j;
      register char *pn, *px, *py;
30
      for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
          *pn = ' ';
      for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
          if (*py == ' ' || *py == '-')
35             *pn = ' ';
          else {
              if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                  j = (i < 0)? -i : i;
                  for (px = pn; j /= 10, px--)
40                     *px = j%10 + '0';
                  if (i < 0)
                      *px = '-';
              }
              else
45                 *pn = ' ';
              i++;
          }
      }
      *pn = '\0';
      nc[ix] = i;
      for (pn = nline; *pn; pn++)
          (void) putc(*pn, fx);
      (void) putc('\n', fx);
50  }

55  /*
   * put out a line (name, [num], seq, [num]): dumpblock()
   */
   static
   putline(ix)
60  {
      int      ix;

```

putline

Table 1 (cont')**...putline**

```

5      int          i;
      register char *px;

      for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
          (void) putc(*px, fx);
10     for (; i < lmax+P_SPC; i++)
          (void) putc(' ', fx);

      /* these count from 1:
      * ni[ ] is current element (from 1)
      * nc[ ] is number at start of current line
15     */
      for (px = out[ix]; *px; px++)
          (void) putc(*px&0x7F, fx);
      (void) putc('\n', fx);
20 }

/*
 * put a line of stars (seqs always in out[0], out[1]): dumpblock()
 */
25 static
stars()
{
    int          i;
30     register char *p0, *p1, cx, *px;

    if (!*out[0] || (*out[0] == ' ' && *(p0[0]) == ' ') ||
        !*out[1] || (*out[1] == ' ' && *(p0[1]) == ' '))
        return;
35     px = star;
    for (i = lmax+P_SPC; i; i--)
        *px++ = ' ';

    for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
40         if (isalpha(*p0) && isalpha(*p1)) {

                if (xbm[*p0-'A']&xbm[*p1-'A']) {
                        cx = '*';
                        nm++;
45                 }
                else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
                        cx = '.';
                else
                        cx = ' ';
50         }
        else
                cx = ' ';
        *px++ = cx;
55     }
    *px++ = '\n';
    *px = '\0';
}
60

```

Table 1 (cont')

```

/*
 * strip path or prefix from pn, return len: pr_align()
 */
5  static
  stripname(pn)
      stripname
      char *pn; /* file name (may be path) */
10 {
      register char *px, *py;

      py = 0;
      for (px = pn; *px; px++)
          if (*px == '/')
15              py = px + 1;
      if (py)
          (void) strcpy(pn, py);
      return(strlen(pn));
20 }

```

25

30

35

40

45

50

55

60

Table 1 (cont')

```

/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
5  * g_calloc() -- calloc() with error checkin
 * readjumps() -- get the good jumps, from tmp file if necessary
 * writejumps() -- write a filled array of jumps to a tmp file: nw()
 */
#include "nw.h"
10 #include <sys/file.h>

char    *jname = "/tmp/homgXXXXXX";          /* tmp file for jumps */
FILE    *fj;

15 int    cleanup();                          /* cleanup tmp file */
long    lseek();

/*
 * remove any tmp file if we blow
20 */
cleanup(i)
    int    i;
{
    if (fj)
25         (void) unlink(jname);
    exit(i);
}

/*
30 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
char    *
35 getseq(file, len)
    char    *file;    /* file name */
    int     *len;     /* seq len */
{
    char    line[1024], *pseq;
40     register char    *px, *py;
    int     natgc, tlen;
    FILE    *fp;

    if ((fp = fopen(file, "r")) == 0) {
45         fprintf(stderr, "%s: can't read %s\n", prog, file);
        exit(1);
    }
    tlen = natgc = 0;
    while (fgets(line, 1024, fp)) {
50         if (*line == ';' || *line == '<' || *line == '>')
            continue;
        for (px = line; *px != '\n'; px++)
            if (isupper(*px) || islower(*px))
                tlen++;
55     }
    if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
        fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
        exit(1);
    }
60     pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';

```

Table 1 (cont')**...getseq**

```

py = pseq + 4;
*len = tlen;
rewind(fp);

while (fgets(line, 1024, fp)) {
    if (*line == ';' || *line == '<' || *line == '>')
        continue;
    for (px = line; *px != '\n'; px++) {
        if (isupper(*px))
            *py++ = *px;
        else if (islower(*px))
            *py++ = toupper(*px);
        if (index("ATGCU", *(py-1)))
            natgc++;
    }
    *py++ = '\0';
    *py = '\0';
    (void) fclose(fp);
    dna = natgc > (tlen/3);
    return(pseq+4);
}

char *
g_calloc(msg, nx, sz)
char *msg;          /* program, calling routine */
int nx, sz;          /* number and size of elements */
{
    char *px, *calloc();

    if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
        if (*msg) {
            fprintf(stderr, "%s: g_calloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
            exit(1);
        }
    }
    return(px);
}

/*
 * get final jmps from dx[ ] or tmp file, set pp[ ], reset dmax: main()
 */
readjumps()
{
    readjumps
    {
        int fd = -1;
        int siz, i0, i1;
        register i, j, xx;

        if (fj) {
            (void) fclose(fj);
            if ((fd = open(jname, O_RDONLY, 0)) < 0) {
                fprintf(stderr, "%s: can't open() %s\n", prog, jname);
                cleanup(1);
            }
        }
        for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
            while (1) {
                for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                    ;
            }
        }
    }
}

```

g_calloc

Table 1 (cont')**...readjumps**

```

5         if (j < 0 && dx[dmax].offset && fj) {
            (void) lseek(fd, dx[dmax].offset, 0);
            (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
            (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
            dx[dmax].ijmp = MAXJMP-1;
        }
10        else
            break;
    }
    if (i >= JMPS) {
        fprintf(stderr, "%s: too many gaps in alignment\n", prog);
        cleanup(1);
    }
15    if (j >= 0) {
        siz = dx[dmax].jp.n[j];
        xx = dx[dmax].jp.x[j];
        dmax += siz;
20        if (siz < 0) { /* gap in second seq */
            pp[1].n[i1] = -siz;
            xx += siz;
            /* id = xx - yy + len1 - 1
            */
25            pp[1].x[i1] = xx - dmax + len1 - 1;
            gapy++;
            ngapy -= siz;
        /* ignore MAXGAP when doing endgaps */
            siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
            i1++;
30        }
        else if (siz > 0) { /* gap in first seq */
            pp[0].n[i0] = siz;
            pp[0].x[i0] = xx;
35            gapx++;
            ngapx += siz;
        /* ignore MAXGAP when doing endgaps */
            siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
            i0++;
40        }
    }
    else
        break;
}

45    /* reverse the order of jumps
    */
    for (j = 0, i0--; j < i0; j++, i0--) {
        i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
50        i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
    }
    for (j = 0, i1--; j < i1; j++, i1--) {
        i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
        i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
55    }
    if (fd >= 0)
        (void) close(fd);
    if (fj) {
        (void) unlink(jname);
60        fj = 0;
        offset = 0;
    }
}

```

Table 1 (cont')

```

5  /*
   * write a filled jmp struct offset of the prev one (if any): nw()
   */
writejumps(ix)
      writejumps
      int      ix;
10  {
      char      *mktemp();

      if (!fj) {
          if (mktemp(jname) < 0) {
15              fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
              cleanup(1);
          }
          if ((fj = fopen(jname, "w")) == 0) {
              fprintf(stderr, "%s: can't write %s\n", prog, jname);
20              exit(1);
          }
      }
      (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
      (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
25  }

```

Table 2

5 PRO XXXXXXXXXXXXXXXX (Length = 15 amino acids)
 Comparison Protein XXXXXYYYYYYY (Length = 12 amino acids)
 % amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as
 10 determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =
 5 divided by 15 = 33.3%

Table 3

15 PRO XXXXXXXXXX (Length = 10 amino acids)
 Comparison Protein XXXXXYYYYYYZZYZ (Length = 15 amino acids)
 % amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as
 20 determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =
 5 divided by 10 = 50%

Table 4

25 PRO-DNA NNNNNNNNNNNNNN (Length = 14 nucleotides)
 Comparison DNA NNNNNNLLLLLLLLLL (Length = 16 nucleotides)

% nucleic acid sequence identity =

30 (the number of identically matching nucleotides between the two nucleic acid sequences as determined by
 ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =
 6 divided by 14 = 42.9%

Table 5

35 PRO-DNA NNNNNNNNNNNN (Length = 12 nucleotides)
 Comparison DNA NNNNLLLVV (Length = 9 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

5 4 divided by 12 = 33.3%

II. Compositions and Methods of the Invention

A. Full-Length PRO Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding
10 polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding various PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. However, for sake of simplicity, in the present specification the protein encoded by the full length native nucleic acid molecules disclosed herein as well as all further native homologues and variants included in the foregoing definition of PRO, will be referred to as "PRO/number", regardless of their
15 origin or mode of preparation.

As disclosed in the Examples below, various cDNA clones have been disclosed. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

20 B. PRO Polypeptide Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of
25 the PRO, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native full-length sequence PRO or in various domains of the PRO described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a
30 substitution, deletion or insertion of one or more codons encoding the PRO that results in a change in the amino acid sequence of the PRO as compared with the native sequence PRO. Optionally, the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of
35 homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally

be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

PRO polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the PRO polypeptide.

PRO fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR.

Preferably, PRO polypeptide fragments share at least one biological and/or immunological activity with the native PRO polypeptide disclosed herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

	Original Residue	Exemplary Substitutions	Preferred Substitutions
5	Ala (A)	val; leu; ile	val
	Arg (R)	lys; gln; asn	lys
	Asn (N)	gln; his; lys; arg	gln
	Asp (D)	glu	glu
10	Cys (C)	ser	ser
	Gln (Q)	asn	asn
	Glu (E)	asp	asp
	Gly (G)	pro; ala	ala
	His (H)	asn; gln; lys; arg	arg
15	Ile (I)	leu; val; met; ala; phe; norleucine	leu
	Leu (L)	norleucine; ile; val; met; ala; phe	ile
	Lys (K)	arg; gln; asn	arg
20	Met (M)	leu; phe; ile	leu
	Phe (F)	leu; val; ile; ala; tyr	leu
	Pro (P)	ala	ala
	Ser (S)	thr	thr
	Thr (T)	ser	ser
25	Trp (W)	tyr; phe	tyr
	Tyr (Y)	trp; phe; thr; ser	phe
	Val (V)	ile; leu; met; phe; ala; norleucine	leu

30 Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- 35 (1) hydrophobic: norleucine, met, ala, val, leu, ile;
 (2) neutral hydrophilic: cys, ser, thr;
 (3) acidic: asp, glu;
 (4) basic: asn, gln, his, lys, arg;
 (5) residues that influence chain orientation: gly, pro; and
 40 (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

45 The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl. Acids Res., 13:4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells et al., Gene, 34:315 (1985)], restriction selection mutagenesis [Wells et al., Philos.

Trans. R. Soc. London SerA, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

C. Modifications of PRO

Covalent modifications of PRO are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO. Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

Other modifications include deamidation of glutamyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by,

one or more serine or threonine residues to the native sequence PRO (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

5 Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

10 Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth.
15 Enzymol., 138:350 (1987).

 Another type of covalent modification of PRO comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

20 The PRO of the present invention may also be modified in a way to form a chimeric molecule comprising PRO fused to another, heterologous polypeptide or amino acid sequence.

 In one embodiment, such a chimeric molecule comprises a fusion of the PRO with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO. The presence of such epitope-tagged
25 forms of the PRO can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag
30 polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an alpha-tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al.,
35 Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

 In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric

molecule (also referred to as an “immunoadhesin”), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

D. Preparation of PRO

The description below relates primarily to production of PRO by culturing cells transformed or transfected with a vector containing PRO nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO. For instance, the PRO sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., **85**:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO.

1. Isolation of DNA Encoding PRO

DNA encoding PRO may be obtained from a cDNA library prepared from tissue believed to possess the PRO mRNA and to express it at a detectable level. Accordingly, human PRO DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the PRO or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO is to use PCR methodology [Sambrook et al., *supra*; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ³²P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., *supra*.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence

databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, CaCl_2 , CaPO_4 , liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*,

Erwinia, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan'*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan'*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for PRO-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilae* (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., Biochem. Biophys. Res. Commun., 112:284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4:475-479 [1985]). Methylotropic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylotrophs, 269 (1982).

Suitable host cells for the expression of glycosylated PRO are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary

(CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen. Virol., 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding PRO may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The PRO may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c)

supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature, 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β -lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid promoters such as the *tac* promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding PRO.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

PRO transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to

300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the PRO coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope.

5. Purification of Polypeptide

Forms of PRO may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO produced.

E. Tissue Distribution

The location of tissues expressing the PRO can be identified by determining mRNA expression in various human tissues. The location of such genes provides information about which tissues are most likely to be affected by the stimulating and inhibiting activities of the PRO polypeptides. The location of a gene in a specific tissue also provides sample tissue for the activity blocking assays discussed below.

As noted before, gene expression in various tissues may be measured by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, *Proc. Natl. Acad. Sci. USA*, 77:5201-5205 [1980]), dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes.

Gene expression in various tissues, alternatively, may be measured by immunological methods, such as immunohistochemical staining of tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence of a PRO polypeptide or against a synthetic peptide based on the DNA sequences encoding the PRO polypeptide or against an exogenous sequence fused to a DNA encoding a PRO polypeptide and encoding a specific antibody epitope. General techniques for generating antibodies, and special protocols for Northern blotting and *in situ* hybridization are provided below.

F. Antibody Binding Studies

The activity of the PRO polypeptides can be further verified by antibody binding studies, in which the ability of anti-PRO antibodies to inhibit the effect of the PRO polypeptides, respectively, on tissue cells is tested. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies, the preparation of which will be described hereinbelow.

Antibody binding studies may be carried out in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. Zola, *Monoclonal Antibodies: A Manual of Techniques*, pp.147-158 (CRC Press, Inc., 1987).

Competitive binding assays rely on the ability of a labeled standard to compete with the test sample analyte for binding with a limited amount of antibody. The amount of target protein in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies preferably are insolubilized before or after the competition, so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte which remain unbound.

Sandwich assays involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected. In a sandwich assay, the test sample analyte is bound by a first antibody which is immobilized on a solid support, and thereafter a second antibody binds to the analyte, thus forming an insoluble three-part complex. See, *e.g.*, US Pat No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assay). For example, one type of sandwich assay is an ELISA assay, in which case the detectable moiety is an enzyme.

For immunohistochemistry, the tissue sample may be fresh or frozen or may be embedded in paraffin and fixed with a preservative such as formalin, for example.

G. Cell-Based Assays

Cell-based assays and animal models for immune related diseases can be used to further understand the relationship between the genes and polypeptides identified herein and the development and pathogenesis of immune related disease.

In a different approach, cells of a cell type known to be involved in a particular immune related disease are transfected with the cDNAs described herein, and the ability of these cDNAs to stimulate or inhibit immune function is analyzed. Suitable cells can be transfected with the desired gene, and monitored for immune function activity. Such transfected cell lines can then be used to test the ability of poly- or monoclonal antibodies or antibody compositions to inhibit or stimulate immune function, for example to modulate monocyte/macrophage proliferation or inflammatory cell infiltration. Cells transfected with the coding sequences of the genes identified herein can further be used to identify drug candidates for the treatment of immune related diseases.

In addition, primary cultures derived from transgenic animals (as described below) can be used in the cell-based assays herein, although stable cell lines are preferred. Techniques to derive continuous cell lines from transgenic animals are well known in the art (see, *e.g.*, Small *et al.*, *Mol. Cell. Biol.* 5: 642-648 [1985]).

The use of an agonist stimulating compound has also been validated experimentally. Activation of 4-1BB by treatment with an agonist anti-4-1BB antibody enhances eradication of tumors. Hellstrom, I. and Hellstrom, K. E., *Crit. Rev. Immunol.* (1998) 18:1. Immunoadjuvant therapy for treatment of tumors, described in more detail below, is another example of the use of the stimulating compounds of the invention.

Alternatively, an immune stimulating or enhancing effect can also be achieved by administration of a PRO which has vascular permeability enhancing properties. Enhanced vascular permeability would be beneficial to disorders which can be attenuated by local infiltration of immune cells (*e.g.*, monocytes/macrophages, eosinophils, PMNs) and inflammation.

On the other hand, PRO polypeptides, as well as other compounds of the invention, which are direct inhibitors of monocyte/macrophage proliferation/activation, lymphokine secretion, and/or vascular permeability can be directly used to suppress the immune response. These compounds are useful to reduce the degree of the immune response and to treat immune related diseases characterized by a hyperactive, superoptimal, or autoimmune response. The use of compound which suppress vascular permeability would be expected to reduce inflammation. Such uses would be beneficial in treating conditions associated with excessive inflammation.

Alternatively, compounds, *e.g.*, antibodies, which bind to stimulating PRO polypeptides and block the stimulating effect of these molecules produce a net inhibitory effect and can be used to suppress the monocyte/macrophage mediated immune response by inhibiting monocyte/macrophage proliferation/activation and/or lymphokine secretion. Blocking the stimulating effect of the polypeptides suppresses the immune response of the mammal.

H. Animal Models

The results of the cell based *in vitro* assays can be further verified using *in vivo* animal models and assays for monocyte/macrophage function. A variety of well known animal models can be used to further understand the role of the genes identified herein in the development and pathogenesis of immune related disease, and to test the efficacy of candidate therapeutic agents, including antibodies, and other antagonists of the native polypeptides, including small molecule antagonists. The *in vivo* nature of such models makes them predictive of responses in human patients. Animal models of immune related diseases include both non-recombinant and recombinant (transgenic) animals. Non-recombinant animal models include, for example, rodent, *e.g.*, murine models. Such models can be generated by introducing cells into syngeneic mice using standard techniques, *e.g.*, subcutaneous injection, tail vein injection, spleen implantation, intraperitoneal implantation, implantation under the renal capsule, *etc.*

Graft-versus-host disease occurs when immunocompetent cells are transplanted into immunosuppressed or tolerant patients. The donor cells recognize and respond to host antigens. The response can vary from life threatening severe inflammation to mild cases of diarrhea and weight loss. Graft-versus-host disease models provide a means of assessing monocyte/macrophage reactivity against MHC antigens and minor transplant antigens. A suitable procedure is described in detail in Current Protocols in Immunology, above, unit 4.3.

Animal models for delayed type hypersensitivity provides an assay of cell mediated immune function as well. In chronic Delayed type hypersensitivity (DTH) reactions, monocytes that have differentiated into macrophages lead to the destruction of host tissue which is replaced by fibrous tissue (fibrosis).

Contact hypersensitivity is a simple delayed type hypersensitivity *in vivo* assay of cell mediated immune function. In this procedure, cutaneous exposure to exogenous haptens which gives rise to a delayed type hypersensitivity reaction which is measured and quantitated. Contact sensitivity involves an initial sensitizing phase followed by an elicitation phase. The elicitation phase occurs when the T lymphocytes encounter an antigen to which they have had previous contact. Swelling and inflammation occur, making this an excellent model of human allergic contact dermatitis. At this point, monocytes leave the blood and differentiate into macrophages. A suitable procedure is described in detail in *Current Protocols in Immunology*, Eds. J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach and W. Strober, John Wiley & Sons, Inc., 1994, unit 4.2. See also Grabbe, S. and Schwarz, T, *Immun. Today* 19 (1): 37-44 (1998)

Recombinant (transgenic) animal models can be engineered by introducing the coding portion of the genes identified herein into the genome of animals of interest, using standard techniques for producing transgenic animals. Animals that can serve as a target for transgenic manipulation include, without limitation, mice, rats, rabbits, guinea pigs, sheep, goats, pigs, and non-human primates, *e.g.*, baboons, chimpanzees and monkeys. Techniques known in the art to introduce a transgene into such animals include pronucleic microinjection (Hoppe and Wanger, U.S. Patent No. 4,873,191); retrovirus-mediated gene transfer into germ lines (*e.g.*, Van der Putten *et al.*, *Proc. Natl. Acad. Sci. USA* 82, 6148-615 [1985]); gene targeting in embryonic stem cells (Thompson *et al.*, *Cell* 56, 313-321 [1989]); electroporation of embryos (Lo, *Mol. Cel. Biol.* 3, 1803-1814 [1983]); sperm-mediated gene transfer (Lavitrano *et al.*, *Cell* 57, 717-73 [1989]). For review, see, for example, U.S. Patent No. 4,736,866.

For the purpose of the present invention, transgenic animals include those that carry the transgene only in part of their cells ("mosaic animals"). The transgene can be integrated either as a single transgene, or in concatamers, *e.g.*, head-to-head or head-to-tail tandems. Selective introduction of a transgene into a particular cell type is also possible by following, for example, the technique of Lasko *et al.*, *Proc. Natl. Acad. Sci. USA* 89, 6232-636 (1992).

The expression of the transgene in transgenic animals can be monitored by standard techniques. For example, Southern blot analysis or PCR amplification can be used to verify the integration of the transgene. The level of mRNA expression can then be analyzed using techniques such as *in situ* hybridization, Northern blot analysis, PCR, or immunocytochemistry.

The animals may be further examined for signs of immune disease pathology, for example by histological examination to determine infiltration of immune cells into specific tissues. Blocking experiments can also be performed in which the transgenic animals are treated with the compounds of the invention to determine the extent of the monocytes/macrophage proliferation stimulation or inhibition of the compounds. In these experiments, blocking antibodies which bind to the PRO polypeptide, prepared as described above, are administered to the animal and the effect on immune function is determined.

Alternatively, "knock out" animals can be constructed which have a defective or altered gene encoding a polypeptide identified herein, as a result of homologous recombination between the endogenous gene encoding the polypeptide and altered genomic DNA encoding the same polypeptide introduced into

an embryonic cell of the animal. For example, cDNA encoding a particular polypeptide can be used to clone genomic DNA encoding that polypeptide in accordance with established techniques. A portion of the genomic DNA encoding a particular polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see *e.g.*, Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see *e.g.*, Li *et al.*, *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse or rat) to form aggregation chimeras [see *e.g.*, Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the polypeptide.

I. ImmunoAdjuvant Therapy

In one embodiment, the immunostimulating compounds of the invention can be used in immunoadjuvant therapy for the treatment of tumors (cancer). It is now well established that monocytes/macrophages recognize human tumor specific antigens. One group of tumor antigens, encoded by the MAGE, BAGE and GAGE families of genes, are silent in all adult normal tissues, but are expressed in significant amounts in tumors, such as melanomas, lung tumors, head and neck tumors, and bladder carcinomas. DeSmet, C. *et al.*, (1996) *Proc. Natl. Acad. Sci. USA*, 93:7149. It has been shown that stimulation of immune cells induces tumor regression and an antitumor response both *in vitro* and *in vivo*. Melero, I. *et al.*, *Nature Medicine* (1997) 3:682; Kwon, E. D. *et al.*, *Proc. Natl. Acad. Sci. USA* (1997) 94: 8099; Lynch, D. H. *et al.*, *Nature Medicine* (1997) 3:625; Finn, O. J. and Lotze, M. T., *J. Immunol.* (1998) 21:114. The stimulatory compounds of the invention can be administered as adjuvants, alone or together with a growth regulating agent, cytotoxic agent or chemotherapeutic agent, to stimulate monocyte/macrophage proliferation/activation and an antitumor response to tumor antigens. The growth regulating, cytotoxic, or chemotherapeutic agent may be administered in conventional amounts using known administration regimes. Immunostimulating activity by the compounds of the invention allows reduced amounts of the growth regulating, cytotoxic, or chemotherapeutic agents thereby potentially lowering the toxicity to the patient.

J. Screening Assays for Drug Candidates

Screening assays for drug candidates are designed to identify compounds that bind to or complex with the polypeptides encoded by the genes identified herein or a biologically active fragment thereof, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such

screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds, including peptides, preferably soluble peptides, (poly)peptide-immunoglobulin fusions, and, in particular, antibodies including, without limitation, poly-
5 and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art. All assays are common in that they call for contacting the drug candidate with a polypeptide encoded
10 by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, *e.g.*, on a microtiter plate, by covalent or non-covalent
15 attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the polypeptide and drying. Alternatively, an immobilized antibody, *e.g.*, a monoclonal antibody, specific for the polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, *e.g.*, the coated surface containing the anchored component. When
20 the reaction is complete, the non-reacted components are removed, *e.g.*, by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labelled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular protein encoded by a gene identified herein, its interaction with that protein can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields
30 and co-workers [Fields and Song, *Nature (London)* 340, 245-246 (1989); Chien *et al.*, *Proc. Natl. Acad. Sci. USA* 88, 9578-9582 (1991)] as disclosed by Chevray and Nathans, *Proc. Natl. Acad. Sci. USA* 89, 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, while the other one functioning as the transcription activation domain. The yeast expression system described in the foregoing publications
35 (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4

activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for β -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

In order to find compounds that interfere with the interaction of a gene identified herein and other intra- or extracellular components can be tested, a reaction mixture is usually prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a test compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described above. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

K. Compositions and Methods for the Treatment of Immune Related Diseases

The compositions useful in the treatment of immune related diseases include, without limitation, proteins, antibodies, small organic molecules, peptides, phosphopeptides, antisense and ribozyme molecules, triple helix molecules, *etc.* that inhibit or stimulate immune function, for example, monocyte proliferation/activation, lymphokine release, or immune cell infiltration.

For example, antisense RNA and RNA molecules act to directly block the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation initiation site, *e.g.*, between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, *e.g.*, Rossi, *Current Biology* 4, 469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple helix formation via Hoogsteen base pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, *e.g.*, PCT publication No. WO 97/33551, *supra*.

These molecules can be identified by any or any combination of the screening assays discussed above and/or by any other screening techniques well known for those skilled in the art.

L. Anti-PRO Antibodies

The present invention further provides anti-PRO antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

5 1. Polyclonal Antibodies

The anti-PRO antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or
10 intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM
15 adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

2. Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature,
20 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof.
25 Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103]. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells
30 of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine
35 ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained,

for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63].

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against PRO. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, supra]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies).

The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., supra] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region

so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

3. Human and Humanized Antibodies

The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeven et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)]. The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy,

Alan R. Liss, p. 77 (1985) and Boerner et al., J. Immunol., 147(1):86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks *et al.*, Bio/Technology 10, 779-783 (1992); Lonberg *et al.*, Nature 368 856-859 (1994); Morrison, Nature 368, 812-13 (1994); Fishwild *et al.*, Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

The antibodies may also be affinity matured using known selection and/or mutagenesis methods as described above. Preferred affinity matured antibodies have an affinity which is five times, more preferably 10 times, even more preferably 20 or 30 times greater than the starting antibody (generally murine, humanized or human) from which the matured antibody is prepared.

4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities [Milstein and Cuello, Nature, 305:537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker et al., EMBO J., 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered

from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan).

Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')₂ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan *et al.*, Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby *et al.*, J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various technique for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny *et al.*, J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger *et al.*, Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber *et al.*, J. Immunol. 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al.*, J. Immunol. 147:60 (1991).

Exemplary bispecific antibodies may bind to two different epitopes on a given PRO polypeptide herein. Alternatively, an anti-PRO polypeptide arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular PRO polypeptide. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express a particular PRO polypeptide. These antibodies possess a PRO-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the PRO polypeptide and further binds tissue factor (TF).

5. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptoputyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

6. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.* Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.*, Anti-Cancer Drug Design, 3: 219-230 (1989).

7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain,

nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcumin, croton, saponaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the
5 tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi , ^{131}I , ^{131}In , ^{90}Y , and ^{186}Re .

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as
10 disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, **238**: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-
15 methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then
20 administration of a "ligand" (*e.g.*, avidin) that is conjugated to a cytotoxic agent (*e.g.*, a radionucleotide).

8. Immunoliposomes

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 3688 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, **77**: 4030
25 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield
30 liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin *et al.*, J. Biol. Chem., **257**: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon *et al.*, J. National Cancer Inst., **81**(19): 1484 (1989).

35 M. Pharmaceutical Compositions

The active PRO molecules of the invention (*e.g.*, PRO polypeptides, anti-PRO antibodies, and/or variants of each) as well as other molecules identified by the screening assays disclosed above, can be administered for the treatment of immune related diseases, in the form of pharmaceutical compositions.

Therapeutic formulations of the active PRO molecule, preferably a polypeptide or antibody of the invention, are prepared for storage by mixing the active molecule having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. [1980]), in the form of lyophilized formulations or aqueous solutions.

Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEENTM, PLURONICSTM or polyethylene glycol (PEG).

Compounds identified by the screening assays disclosed herein can be formulated in an analogous manner, using standard techniques well known in the art.

Lipofections or liposomes can also be used to deliver the PRO molecule into cells. Where antibody fragments are used, the smallest inhibitory fragment which specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable region sequences of an antibody, peptide molecules can be designed which retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology (see, *e.g.*, Marasco *et al.*, *Proc. Natl. Acad. Sci. USA* 90, 7889-7893 [1993]).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise a cytotoxic agent, cytokine or growth inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active PRO molecules may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations or the PRO molecules may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ -ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

N. Methods of Treatment

It is contemplated that the polypeptides, antibodies and other active compounds of the present invention may be used to treat various immune related diseases and conditions, such as monocyte/macrophage diseases, including those characterized by infiltration of inflammatory cells into a tissue, stimulation of monocyte/macrophages, inhibition of monocytes/macrophages, increased or decreased vascular permeability or the inhibition thereof.

Exemplary conditions or disorders to be treated with the polypeptides, antibodies and other compounds of the invention, include, but are not limited to systemic lupus erythematosus, rheumatoid arthritis, juvenile chronic arthritis, osteoarthritis, spondyloarthropathies, systemic sclerosis (scleroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis), diabetes mellitus, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis), demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease (ulcerative colitis: Crohn's disease), gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and

urticaria, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft - versus-host-disease.

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that mainly involves the synovial membrane of multiple joints with resultant injury to the articular cartilage. The pathogenesis is T lymphocyte dependent and is associated with the production of rheumatoid factors, auto-antibodies directed against self IgG, with the resultant formation of immune complexes that attain high levels in joint fluid and blood. These complexes in the joint may induce the marked infiltrate of lymphocytes and monocytes/macrophages into the synovium and subsequent marked synovial changes; the joint space/fluid is infiltrated by similar cells with the addition of numerous neutrophils. Tissues affected are primarily the joints, often in symmetrical pattern. However, extra-articular disease also occurs in two major forms. One form is the development of extra-articular lesions with ongoing progressive joint disease and typical lesions of pulmonary fibrosis, vasculitis, and cutaneous ulcers. The second form of extra-articular disease is the so called Felty's syndrome which occurs late in the RA disease course, sometimes after joint disease has become quiescent, and involves the presence of neutropenia, thrombocytopenia and splenomegaly. This can be accompanied by vasculitis in multiple organs with formations of infarcts, skin ulcers and gangrene. Patients often also develop rheumatoid nodules in the subcutis tissue overlying affected joints; the nodules late stage have necrotic centers surrounded by a mixed inflammatory cell infiltrate. Other manifestations which can occur in RA include: pericarditis, pleuritis, coronary arteritis, interstitial pneumonitis with pulmonary fibrosis, keratoconjunctivitis sicca, and rheumatoid nodules. The number and activation state of macrophages in the inflamed synovium correlates with the significance of RA (Kinne et al., 2000 Arthritis Res. 2: 189-202). As described above, macrophages are not believed to be involved in the early events of RA, but monocytes/macrophages have tissue destructive and tissue remodeling properties which may contribute to both acute and chronic RA.

Juvenile chronic arthritis is a chronic idiopathic inflammatory disease which begins often at less than 16 years of age. Its phenotype has some similarities to RA; some patients which are rheumatoid factor positive are classified as juvenile rheumatoid arthritis. The disease is sub-classified into three major categories: pauciarticular, polyarticular, and systemic. The arthritis can be severe and is typically destructive and leads to joint ankylosis and retarded growth. Other manifestations can include chronic anterior uveitis and systemic amyloidosis.

Spondyloarthropathies are a group of disorders with some common clinical features and the common association with the expression of HLA-B27 gene product. The disorders include: ankylosing spondylitis, Reiter's syndrome (reactive arthritis), arthritis associated with inflammatory bowel disease, spondylitis associated with psoriasis, juvenile onset spondyloarthropathy and undifferentiated spondyloarthropathy. Distinguishing features include sacroileitis with or without spondylitis; inflammatory asymmetric arthritis; association with HLA-B27 (a serologically defined allele of the HLA-B locus of class I MHC); ocular inflammation, and absence of autoantibodies associated with other rheumatoid disease. It was shown that CD163+ macrophages were increased in the synovial lining and

colonic mucosa in Spondyloarthropathy and correlates with the expression of HLA-DR and the production of TNF-alpha (Baeten et al., 2002 J Pathol 196(3):343-350).

Systemic sclerosis (scleroderma) has an unknown etiology. A hallmark of the disease is induration of the skin; likely this is induced by an active inflammatory process. Scleroderma can be localized or systemic; vascular lesions are common and endothelial cell injury in the microvasculature is an early and important event in the development of systemic sclerosis; the vascular injury may be immune mediated. An immunologic basis is implied by the presence of mononuclear cell infiltrates in the cutaneous lesions and the presence of anti-nuclear antibodies in many patients. ICAM-1 is often upregulated on the cell surface of fibroblasts in skin lesions suggesting that T cell interaction with these cells may have a role in the pathogenesis of the disease. As well as T cells, monocytes/macrophages are proposed to play a role in the progression of scleroderma by secreting fibrogenic cytokines (Yamamoto et al., 2001 J Dermatol Sci 26(2): 133-139). Other organs involved include: the gastrointestinal tract: smooth muscle atrophy and fibrosis resulting in abnormal peristalsis/motility; kidney: concentric subendothelial intimal proliferation affecting small arcuate and interlobular arteries with resultant reduced renal cortical blood flow, results in proteinuria, azotemia and hypertension; skeletal muscle: atrophy, interstitial fibrosis; inflammation; lung: interstitial pneumonitis and interstitial fibrosis; and heart: contraction band necrosis, scarring/fibrosis.

Idiopathic inflammatory myopathies including dermatomyositis, polymyositis and others are disorders of chronic muscle inflammation of unknown etiology resulting in muscle weakness. Muscle injury/inflammation is often symmetric and progressive. Autoantibodies are associated with most forms. These myositis-specific autoantibodies are directed against and inhibit the function of components, proteins and RNA's, involved in protein synthesis.

Sjögren's syndrome is due to immune-mediated inflammation and subsequent functional destruction of the tear glands and salivary glands. The disease can be associated with or accompanied by inflammatory connective tissue diseases. The disease is associated with autoantibody production against Ro and La antigens, both of which are small RNA-protein complexes. Lesions result in keratoconjunctivitis sicca, xerostomia, with other manifestations or associations including biliary cirrhosis, peripheral or sensory neuropathy, and palpable purpura.

Systemic vasculitis are diseases in which the primary lesion is inflammation and subsequent damage to blood vessels which results in ischemia/necrosis/degeneration to tissues supplied by the affected vessels and eventual end-organ dysfunction in some cases. Vasculitis can also occur as a secondary lesion or sequelae to other immune-inflammatory mediated diseases such as rheumatoid arthritis, systemic sclerosis, *etc.*, particularly in diseases also associated with the formation of immune complexes. Diseases in the primary systemic vasculitis group include: systemic necrotizing vasculitis: polyarteritis nodosa, allergic angiitis and granulomatosis, polyangiitis; Wegener's granulomatosis; lymphomatoid granulomatosis; and giant cell arteritis. Miscellaneous vasculitides include: mucocutaneous lymph node syndrome (MLNS or Kawasaki's disease), isolated CNS vasculitis, Behet's disease, thromboangiitis obliterans (Buerger's disease) and cutaneous necrotizing venulitis. The pathogenic mechanism of most of

the types of vasculitis listed is believed to be primarily due to the deposition of immunoglobulin complexes in the vessel wall and subsequent induction of an inflammatory response either via ADCC, complement activation, or both.

Sarcoidosis is a condition of unknown etiology which is characterized by the presence of epithelioid granulomas in nearly any tissue in the body; involvement of the lung is most common. The pathogenesis involves the persistence of activated macrophages and lymphoid cells at sites of the disease with subsequent chronic sequelae resultant from the release of locally and systemically active products released by these cell types.

Autoimmune hemolytic anemia including autoimmune hemolytic anemia, immune pancytopenia, and paroxysmal nocturnal hemoglobinuria is a result of production of antibodies that react with antigens expressed on the surface of red blood cells (and in some cases other blood cells including platelets as well) and is a reflection of the removal of those antibody coated cells via complement mediated lysis and/or ADCC/Fc-receptor-mediated mechanisms.

Thyroiditis including Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, and atrophic thyroiditis, are the result of an autoimmune response against thyroid antigens with production of antibodies that react with proteins present in and often specific for the thyroid gland. Experimental models exist including spontaneous models: rats (BUF and BB rats) and chickens (obese chicken strain); inducible models: immunization of animals with either thyroglobulin, thyroid microsomal antigen (thyroid peroxidase).

Inflammatory and Fibrotic Lung Disease, including Eosinophilic Pneumonias; Idiopathic Pulmonary Fibrosis, and Hypersensitivity Pneumonitis may involve a dysregulated immune-inflammatory response. Inhibition of that response would be of therapeutic benefit.

Psoriasis is a T lymphocyte-mediated inflammatory disease. Lesions contain infiltrates of T lymphocytes, macrophages and antigen processing cells, and some neutrophils.

Other diseases in which intervention of the immune and/or inflammatory response have benefit are infectious disease including but not limited to viral infection (including but not limited to AIDS, hepatitis A, B, C, D, E and herpes) bacterial infection, fungal infections, and protozoal and parasitic infections. Molecules (or derivatives/agonists) which stimulate the immune reaction can be utilized therapeutically to enhance the immune response to infectious agents), diseases of immunodeficiency (molecules/derivatives/agonists) which stimulate the immune reaction can be utilized therapeutically to enhance the immune response for conditions of inherited, acquired, infectious induced (as in HIV infection), or iatrogenic (*i.e.*, as from chemotherapy) immunodeficiency, and neoplasia.

It has been demonstrated that some human cancer patients develop an antibody and/or monocyte/macrophage response to antigens on neoplastic cells. It has also been shown in animal models of neoplasia that enhancement of the immune response can result in rejection or regression of that particular neoplasm. Molecules that enhance the monocyte/macrophage response have utility *in vivo* in enhancing the immune response against neoplasia. Molecules which enhance the monocyte/macrophage proliferative response (or small molecule agonists or antibodies that affected the same receptor in an

agonistic fashion) can be used therapeutically to treat cancer. Molecules that inhibit the monocyte/macrophage response also function *in vivo* during neoplasia to suppress the immune response to a neoplasm; such molecules can either be expressed by the neoplastic cells themselves or their expression can be induced by the neoplasm in other cells. Antagonism of such inhibitory molecules (either with
5 antibody, small molecule antagonists or other means) enhances immune-mediated tumor rejection.

Additionally, inhibition of molecules with proinflammatory properties may have therapeutic benefit in reperfusion injury; stroke; myocardial infarction; atherosclerosis; acute lung injury; hemorrhagic shock; burn; sepsis/septic shock; acute tubular necrosis; endometriosis; degenerative joint disease and pancreatitis.

10 The compounds of the present invention, *e.g.*, polypeptides or antibodies, are administered to a mammal, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation (intranasal, intrapulmonary) routes. Intravenous or inhaled administration of polypeptides and antibodies
15 is preferred.

In immunoadjuvant therapy, other therapeutic regimens, such administration of an anti-cancer agent, may be combined with the administration of the proteins, antibodies or compounds of the instant invention. For example, the patient to be treated with a the immunoadjuvant of the invention may also receive an anti-cancer agent (chemotherapeutic agent) or radiation therapy. Preparation and dosing
20 schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in *Chemotherapy Service* Ed., M.C. Perry, Williams & Wilkins, Baltimore, MD (1992). The chemotherapeutic agent may precede, or follow administration of the immunoadjuvant or may be given simultaneously therewith. Additionally, an anti-estrogen compound
25 such as tamoxifen or an anti-progesterone such as onapristone (see, EP 616812) may be given in dosages known for such molecules.

It may be desirable to also administer antibodies against other immune disease associated or tumor associated antigens, such as antibodies which bind to CD20, CD11a, CD18, ErbB2, EGFR, ErbB3, ErbB4, or vascular endothelial factor (VEGF). Alternatively, or in addition, two or more antibodies
30 binding the same or two or more different antigens disclosed herein may be coadministered to the patient. Sometimes, it may be beneficial to also administer one or more cytokines to the patient. In one embodiment, the PRO polypeptides are coadministered with a growth inhibitory agent. For example, the growth inhibitory agent may be administered first, followed by a PRO polypeptide. However, simultaneous administration or administration first is also contemplated. Suitable dosages for the growth
35 inhibitory agent are those presently used and may be lowered due to the combined action (synergy) of the growth inhibitory agent and the PRO polypeptide.

For the treatment or reduction in the severity of immune related disease, the appropriate dosage of an a compound of the invention will depend on the type of disease to be treated, as defined above, the

severity and course of the disease, whether the agent is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the compound, and the discretion of the attending physician. The compound is suitably administered to the patient at one time or over a series of treatments.

5 For example, depending on the type and severity of the disease, about 1 µg/kg to 15 mg/kg (*e.g.*, 0.1-20 mg/kg) of polypeptide or antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily dosage might range from about 1 µg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is
10 sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

O. Articles of Manufacture

In another embodiment of the invention, an article of manufacture containing materials (*e.g.*, comprising a PRO molecule) useful for the diagnosis or treatment of the disorders described above is
15 provided. The article of manufacture comprises a container and an instruction. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for diagnosing or treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The
20 active agent in the composition is usually a polypeptide or an antibody of the invention. An instruction or label on, or associated with, the container indicates that the composition is used for diagnosing or treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint,
25 including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

P. Diagnosis and Prognosis of Immune Related Disease

Cell surface proteins, such as proteins which are overexpressed in certain immune related diseases, are excellent targets for drug candidates or disease treatment. The same proteins along with secreted proteins encoded by the genes amplified in immune related disease states find additional use in the
30 diagnosis and prognosis of these diseases. For example, antibodies directed against the protein products of genes amplified in multiple sclerosis, rheumatoid arthritis, or another immune related disease, can be used as diagnostics or prognostics.

For example, antibodies, including antibody fragments, can be used to qualitatively or quantitatively detect the expression of proteins encoded by amplified or overexpressed genes ("marker
35 gene products"). The antibody preferably is equipped with a detectable, *e.g.*, fluorescent label, and binding can be monitored by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. These techniques are particularly suitable, if the overexpressed gene encodes a cell surface protein. Such binding assays are performed essentially as described above.

In situ detection of antibody binding to the marker gene products can be performed, for example, by immunofluorescence or immunoelectron microscopy. For this purpose, a histological specimen is removed from the patient, and a labeled antibody is applied to it, preferably by overlaying the antibody on a biological sample. This procedure also allows for determining the distribution of the marker gene product in the tissue examined. It will be apparent for those skilled in the art that a wide variety of histological methods are readily available for *in situ* detection.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

EXAMPLE 1: Microarray analysis of monocyte/macrophages.

Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in diseased tissues as compared to their normal counterparts. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes known to be expressed in certain disease states may be arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (in this instance, differentiated macrophages) sample is greater than hybridization signal of a probe from a control (in this instance, non-differentiated monocytes) sample, the gene or genes expressed in the test tissue are identified. The implication of this result is that an overexpressed protein in a test tissue is useful not only as a diagnostic marker for the presence of the disease condition, but also as a therapeutic target for treatment of the disease condition.

The methodology of hybridization of nucleic acids and microarray technology is well known in the art. In one example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in PCT Patent Application Serial No. PCT/US01/10482, filed on March 30, 2001 and which is herein incorporated by reference.

In this experiment, CD14+ monocytes are selected by positive selection according to Miltenyi MACS™ protocol. Lymphocytes in 100 ml heparinized blood are separated using Ficoll Paque™. Cells are washed twice in PBS/0.5% BSA/2 mM EDTA. In final wash, all gradients are pooled and volume is brought to approximately 10 ml. The cells are centrifuged, the supernatant is removed and the cell pellet

is resuspended in buffer in a total volume of 10^7 cells per 80 μ l buffer. Add 20 μ l CD14 microbeads per 10^7 total cells, mix and incubate 15 minutes at 6-12 C. Wash the cells by adding 20x labeling volume of buffer, spin pellet and resuspend in 500 μ l buffer per 10^8 cells. Separate cells with MACS™ depletion column type D and check purity of cells by labeling with anti-CD45 and anti-CD14 antibodies (cell purity at this point is >95%). Lyse cells in RNA lysis buffer to obtain a timepoint of Day 0 monocytes, then plate remaining cells in 6 well plates in macrophage differentiation medium: DMEM 4.5 μ g/ml glucose, Pen-Strep, L-glutamine, 20% FBS and 10% Human AB serum (Gemini, Cat # 100-512). Seed cells at 1.5×10^6 per well (6 well Costar cell culture plates) and grow at 37 C, 7% CO₂. After 24 hours in culture, the cells were harvested and lysed in RNA lysis buffer to obtain mRNA for the Day 1 timepoint. The remaining cells were kept in culture and until Day 7. After 7 days in culture, the cells were lysed in RNA lysis buffer to obtain Day 7 timepoint at which time the cells displayed gross macrophage morphology.

The mRNA was isolated by Qiagen miniprep and analysis run on Affimax™ (Affymetrix Inc. Santa Clara, CA) microarray chips and proprietary Genentech microarrays. The cells harvested at Day 0 timepoint, the Day 1 timepoint, and the Day 7 timepoint were subjected to the same analysis. Genes were compared whose expression was upregulated at Day 7 as compared to Day 0 and Day 1.

Below are the results of these experiments, demonstrating that various PRO polypeptides of the present invention are differentially expressed in differentiated macrophages at Day 7 as compared to non-differentiated monocytes at Day 0 and at Day 1. As described above, these data demonstrate that the PRO polypeptides of the present invention are useful not only as diagnostic markers for the presence of one or more immune disorders, but also serve as therapeutic targets for the treatment of those immune disorders. Specifically, the cDNAs shown Figures 592, Figure 708, Figure 724, Figure 888, Figure 1095, Figure 1109, Figure 1456 and Figure 2331 are significantly overexpressed in differentiated macrophages as compared to non-differentiated monocytes at Day 0 and Day 1.

The Figures 1-2517 show the nucleic acids of the invention and their encoded PRO polypeptides that are differentially expressed in differentiated macrophages at Day 7 as compared to non-differentiated monocytes at Day 0 and at Day 1.

EXAMPLE 2: Use of PRO as a hybridization probe

The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled PRO-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO can then be identified using standard techniques known in the art.

EXAMPLE 3: Expression of PRO in *E. coli*

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli*.

The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., Gene, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., supra. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH₄)₂SO₄, 0.71 g sodium citrate•2H₂O, 1.07 g KCl, 5 .36 Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO₄) and grown for approximately

20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 4: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook et al., supra. The resulting vector is called pRK5-PRO.

5 In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 μ g pRK5-PRO DNA is mixed with about 1 μ g DNA encoding the VA RNA gene [Thimmappaya et al., Cell, 31:543 (1982)] and dissolved in 500 μ l of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl_2 . To this mixture is added,
10 dropwise, 500 μ l of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO_4 , and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

15 Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 $\mu\text{Ci/ml}$ ^{35}S -cysteine and 200 $\mu\text{Ci/ml}$ ^{35}S -methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO polypeptide. The cultures containing transfected cells may
20 undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Somparyrac et al., Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 μ g pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate
25 is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 $\mu\text{g/ml}$ bovine insulin and 0.1 $\mu\text{g/ml}$ bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column
30 chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as CaPO_4 or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ^{35}S -methionine. After determining the presence of PRO polypeptide, the culture
35 medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 promoter/enhancer containing vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 promoter/enhancer containing vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by Ni²⁺-chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect[®] (Quiagen), Dosper[®] or Fugene[®] (Boehringer Mannheim). The cells are grown as described in Lucas et al., supra. Approximately 3 x 10⁷ cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mL of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 µm filtered PS20 with 5% 0.2 µm diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3 x 10⁵ cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2 x 10⁶ cells/mL. On day 0, pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6

mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μ m filter. The filtrate was either stored at 4°C or immediately loaded onto
5 columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the
10 column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows.

15 The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 μ l of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-
20 His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 5: Expression of PRO in Yeast

25 The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the
30 ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be
35 analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

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EXAMPLE 6: Expression of PRO in Baculovirus-Infected Insect Cells

The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged PRO can then be purified, for example, by Ni²⁺-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl₂; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 µm filter. A Ni²⁺-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A₂₈₀ with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A₂₈₀ baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni²⁺-NTA-conjugated to alkaline phosphatase

(Qiagen). Fractions containing the eluted His₁₀-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

5 Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 7: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind PRO.

10 Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, supra. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms.

15 Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-
20 PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The
25 fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in
30 the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion
35 chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

EXAMPLE 8: Purification of PRO Polypeptides Using Specific Antibodies

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (*e.g.*, high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

EXAMPLE 9: Drug Screening

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested.

Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an

agent with an PRO polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

EXAMPLE 10: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 9: 19-21 (1991)).

In one approach, the three-dimensional structure of the PRO polypeptide, or of a PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon

which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

What is claimed:

1. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide
5 sequence identity to:
 - (a) the nucleotide sequence shown in any one of the Figures 1-2517 (SEQ ID NOS: 1-2517); or
 - (b) the nucleotide sequence encoding the polypeptide shown in any one of the Figures 1-2517 (SEQ ID NOS: 1-2517).
- 10 2. A vector comprising the nucleic acid of Claim 1.
3. The vector of Claim 2 operably linked to control sequences recognized by a host cell transformed with the vector.
- 15 4. A host cell comprising the vector of Claim 2.
5. The host cell of Claim 4, wherein said cell is a CHO cell, an *E.coli* cell or a yeast cell.
- 20 6. A process for producing a PRO polypeptide comprising culturing the host cell of Claim 5 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.
- 25 7. An isolated polypeptide having at least 80% amino acid sequence identity to:
 - (a) a polypeptide shown in any one of Figures 1-2517 (SEQ ID NOS: 1-2517); or
 - (b) a polypeptide encoded by the full length coding region of the nucleotide sequence shown in any one of Figures 1-2517 (SEQ ID NOS: 1-2517).
- 30 8. A chimeric molecule comprising a polypeptide according to Claim 7 fused to a heterologous amino acid sequence.
9. The chimeric molecule of Claim 8, wherein said heterologous amino acid sequence is an epitope tag sequence or an Fc region of an immunoglobulin.
- 35 10. An antibody which specifically binds to a polypeptide according to Claim 7.
11. The antibody of Claim 10, wherein said antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody.

12. A composition of matter comprising (a) a polypeptide of Claim 7, (b) an agonist of said polypeptide, (c) an antagonist of said polypeptide, or (d) an antibody that binds to said polypeptide, in combination with a carrier.

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13. The composition of matter of Claim 12, wherein said carrier is a pharmaceutically acceptable carrier.

14. The composition of matter of Claim 13 comprising a therapeutically effective amount of (a), (b), (c) or (d).

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15. An article of manufacture, comprising:
a container;
a label on said container; and

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a composition of matter comprising (a) a polypeptide of Claim 7, (b) an agonist of said polypeptide, (c) an antagonist of said polypeptide, or (d) an antibody that binds to said polypeptide, contained within said container, wherein label on said container indicates that said composition of matter can be used for treating an immune related disease.

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16. A method of treating an immune related disorder in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of (a) a polypeptide of Claim 7, (b) an agonist of said polypeptide, (c) an antagonist of said polypeptide, or (d) an antibody that binds to said polypeptide.

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17. The method of Claim 16, wherein the immune related disorder is systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, a spondyloarthropathy, systemic sclerosis, an idiopathic inflammatory myopathy, Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, a demyelinating disease of the central or peripheral nervous system, idiopathic demyelinating polyneuropathy, Guillain-Barré syndrome, a chronic inflammatory demyelinating polyneuropathy, a hepatobiliary disease, infectious or autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, Whipple's disease, an autoimmune or immune-mediated skin disease, a bullous skin disease, erythema multiforme, contact dermatitis, psoriasis, an allergic disease, asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity, urticaria, an immunologic disease of the lung, eosinophilic pneumonias, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, a transplantation associated disease, graft rejection or graft-versus-host-disease.

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18. A method for determining the presence of a PRO polypeptide of the invention as described in Figures 1-2517 (SEQ ID NOS: 1-2517), in a sample suspected of containing said polypeptide, said method comprising exposing said sample to an anti-PRO antibody, where the and determining binding of said antibody to a component of said sample.

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19. A method of diagnosing an immune related disease in a mammal, said method comprising detecting the level of expression of a gene encoding a PRO polypeptide of the invention as described in Figures 1-2517 (SEQ ID NOS: 1-2517), (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower level of expression of said gene in the test sample as compared to the control sample is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained.

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20. A method of diagnosing an immune related disease in a mammal, said method comprising (a) contacting a PRO polypeptide of the invention as described in Figures 1-2517 (SEQ ID NOS: 1-2517), anti-PRO antibody with a test sample of tissue cells obtained from said mammal and (b) detecting the formation of a complex between the antibody and the polypeptide in the test sample, wherein formation of said complex is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained.

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21. A method of identifying a compound that inhibits the activity of a PRO polypeptide of the invention as described in Figures 1-2517 (SEQ ID NOS: 1-2517), said method comprising contacting cells which normally respond to said polypeptide with (a) said polypeptide and (b) a candidate compound, and determining the lack responsiveness by said cell to (a).

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22. A method of identifying a compound that inhibits the expression of a gene encoding a PRO polypeptide of the invention as described in Figures 1-2517 (SEQ ID NOS: 1-2517), said method comprising contacting cells which normally express said polypeptide with a candidate compound, and determining the lack of expression said gene.

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23. The method of Claim 22, wherein said candidate compound is an antisense nucleic acid.

24. A method of identifying a compound that mimics the activity of a PRO polypeptide of the invention as described in any one of Figures 1-2517 (SEQ ID NOS: 1-2517), said method comprising contacting cells which normally respond to said polypeptide with a candidate compound, and determining the responsiveness by said cell to said candidate compound.

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25. A method of stimulating the immune response in a mammal, said method comprising administering to said mammal an effective amount of a PRO polypeptide of the invention as described in any one of Figures 1-2517 (SEQ ID NOS: 1-2517), antagonist, wherein said immune response is stimulated.

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26. A method of diagnosing an inflammatory immune response in a mammal, said method comprising detecting the level of expression of a gene encoding a PRO polypeptide of the invention as described in any one of Figures 1-2517 (SEQ ID NOS: 1-2517), (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower level of expression of said gene in the test sample as compared to the control sample is indicative of the presence of an inflammatory immune response in the mammal from which the test tissue cells were obtained.

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27. A method of differentiating monocytes comprising;

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- (a) isolating a population of monocytes;
- (b) contacting the monocytes with an effective amount of a PRO polypeptide of the invention as described in any of of Figures 1-2517 (SEQ ID NOS: 1-2517); and
- (c) determining the differentiation of said monocytes to said PRO polypeptide.

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FIGURE 1

CATCCGGTGTGGTCGACGGGTCCTCCAAGAGTTTGGGGCGCGGACCGGAGTACCTTGCGTGCAGTT**ATGT**CGGCG
TCGGTAGTGTCTGTCAATTCGCGGTTCTTAGAAGAGTACTTGAGCTCCACTCCGCAGCGTCTGAAGTTGCTGGAC
GCGTACCTGCTGTATATACTGCTGACCGGGGCGCTGCAGTTCGGTTACTGTCTCCTCGTGGGGACCTTCCCCCTTC
AACTCTTTTCTCTCGGGCTTCATCTCTTGTGTGGGGAGTTTCATCCTAGCGGTTTGCCTGAGAATACAGATCAAC
CCACAGAACAAAGCGGATTTCCAAGGCATCTCCCCAGAGCGAGCCTTTGCTGATTTTCTCTTTGCCAGCACCATC
CTGCACCTTGTTGTCATGAACCTTTGTTGGC**TGA**ATCATTCTCATTACTTAATTGAGGAGTAGGAGACTAAAAGA
ATGTTCACTCTTTGAATTCCTGGATAAGAGTTCTGGAGATGGCAGCTTATTGGACACATGGATTTTCTTCAGAT
TTGACACTTACTGCTAGCTCTGCTTTTTATGACAGGAGAAAAGCCCAGAGTTCAGTGTGTGTCAGAACAACCTTC
TAACAAACATTTATTAATCCAGCCTCTGCCTTTTATTAAATGTAACCTTTTGCTTTCCAAATTAAAGAACTCCAT
GCCACTCCTCAAAAAAAAAAAAAA

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FIGURE 2

MSASVVSVISRFLEEYLSSTPQRLKLLDAYLLYILLTGALQFGYCLLVGTFFPNSFLSGFISCVGSFILAVCLRI
QINPQNKADFQGISPERAFADFLFASTILHLVVMNFVG

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FIGURE 3

CTCCGGCGCAGTGTGGGACTGTCTGGGTATCGGAAAGCAAGCCTACGTTGCTCACTATTACGTATAATCCTTTT
CTTTTCAAGATGCCTGAGGAAGTGCACCATGGAGAGGAGGAGGTGGAGACTTTTGCCTTTTCAGGCAGAAATTGCC
CAACTCATGTCCCTCATCATCAATACCTTCTATTCCAACAAGGAGATTTTCCTTCGGGAGTTGATCTCTAATGCT
TCTGATGCCTTGGACAAGATTGCTATGAGAGCCTGACAGACCCTTCGAAGTTGGACAGTGGTAAAGAGCTGAAA
ATTGACATCATCCCCAACCTCAGGAACGTACCCTGACTTTGGTAGACACAGGCATTGGCATGACCAAAGCTGAT
CTCATAAATAATTTGGGAACCATTGCCAAGTCTGGTACTAAAGCATTTCATGGAGGCTCTTCAGGCTGGTGCAGAC
ATCTCCATGATTGGGCAGTTTGGTGTGGCTTTTATTCTGCCTACTTGGTGGCAGAGAAAGTGGTTGTGATCACA
AAGCACAACGATGATGAACAGTATGCTTGGGAGTCTTCTGCTGGAGGTTTCCTTCACTGTGCGTGCTGACCATGGT
GAGCCCATTGGCAGGGGTACCAAAGTGATCTCCATCTTAAAGAAGATCAGACAGAGTACCTAGAAGAGAGGCGG
GTCAAAGAAGTAGTGAAGAAGCATTCTCAGTTTCATAGGCTATCCCATCACCTTTTATTGGAGAAGGAACGAGAG
AAGGAAATTAGTGATGATGAGGCAGAGGAAGAGAAAGGTGAGAAAGAAGAGGAAGATAAAGATGATGAAGAAAA
CCCAAGATCGAAGATGTGGGTTTCAGATGAGGAGGATGACAGCGGTAAGGATAAGAAGAAGAAAACCTAAGAAGATC
AAAGAGAAATACATTGATCAGGAAGAACTAAACAAGACCAAGCCTATTTGGACCAGAAACCCTGATGACATCACC
CAAGAGGAGTATGGAGAATTCTACAAGAGCCTCACTAATGACTGGGAAGACCACTTGGCAGTCAAGCACTTTTCT
GTAGAAGGTCAGTTGGAATTCAGGGCATTGCTATTTATTCTCGTGGGCTCCCTTTGACCTTTTTTGAGAACAAG
AAGAAAAAGAACAACATCAAACTCTATGTCCGCCGTGTGTTTCATCATGGACAGCTGTGATGAGTTGATACAGAG
TATCTCAATTTTATCCGTGGTGTGGTTGACTCTGAGGATCTGCCCCGTAACATCTCCCGAGAAATGCTCCAGCAG
AGCAAAATCTTGAAAGTCATTGCAAAAACATTGTTAAGAAGTGCCTTGAGCTCTTCTCTGAGCTGGCAGAAGAC
AAGGAGAATTACAAGAAATTCTATGAGGCATTCTCTAAAAATCTCAAGCTTGGAATCCACGAAGACTCCACTAAC
CGCCGCCGCTGTCTGAGCTGCTGCGCTATCATACCTCCAGTCTGGAGATGAGATGACATCTCTGTGAGAGTAT
GTTTCTCGCATGAAGGAGACACAGAAGTCCATCTATTACATCACTGGTGAGAGCAAAGAGCAGGTGGCCAACTCA
GCTTTTGTGGAGCGAGTGCGGAAACGGGGCTTCGAGGTGGTATATATGACCGAGCCCATTTGACGAGTACTGTGTG
CAGCAGCTCAAGGAATTTGATGGGAAGAGCCTGGTCTCAGTTACCAAGGAGGGTCTGGAGCTGCCTGAGGATGAG
GAGGAGAAGAAGAGATGGAAGAGAGCAAGGCAAGTTTGGAAACCTCTGCAAGCTCATGAAAGAAATCTTAGAT
AAGAAGGTTGAGAAGGTGACAATCTCCAATAGACTTGTGTCTTCACCTTGCTGCATTGTGACCAGCACCTACGGC
TGGACAGCCAATATGGAGCGGATCATGAAAGCCCAGGCACCTTCGGGACAACCTCCACCATGGGCTATATGATGGCC
AAAAAGCACCTGGAGATCAACCCTGACCACCCCATTTGTGGAGACGCTGCGGCAGAAGGCTGAGGCCGACAAGAA
GATAAGGCAGTTAAGGACCTGGTGGTGCTGCTGTTTGAACCGCCCTGCTATCTTCTGGCTTTTCCCTTGAGGAT
CCCCAGACCCACTCCAACCGCATCTATCGCATGATCAAGCTAGGTCTAGGTATTGATGAAGATGAAGTGGCAGCA
GAGGAACCCAATGCTGCAGTTCTGATGAGATCCCCCTCTCGAGGGCGATGAGGATGCGTCTCGCATGGAAGAA
GTCGATTAGGTTAGGAGTTCATAGTTGGAAAACCTTGTGCCCTTGATAGTGTCCCCATGGGCTCCCACTGCAGCC
TCGAGTGCCCCGTGCCACCTGGCTCCCCCTGCTGGTGTCTAGTGTTTTTTCCCTCTCCTGTCTTGTGTTGAA
GGCAGTAAACTAAGGGTGTCAAGCCCCATTCCCTCTCTACTCTTGACAGCAGGATTGGATGTTGTGTATTGTGGT
TTATTTTATTTCTTCATTTTGTCTGAAATTAAAGTATGCAAAATAAAGAATATGCCGTTTTTAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAA

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FIGURE 4

MPEEVHHGEEEVETFAFQAEIAQLMSLIINTFYSNKEIFLRELISNASDALDKIRYESLTDP SKLDSGKELKIDI
IPNPQERTLTTLVDTGIGMTKADLINNLGTIAKSGTKAFMEALQAGADISMIGQFGVGFYSAYLVAEKVVVITKHN
DDEQYAWESSAGGSFTVRADHGEP IGRGTKVILHLKEDQTEYLEERRVKEVVKKHSQFIGYPITLYLEKEREKEI
SDDEAEEEEKGEKEEEDKDDEEKPKIEDVGSDEEDDSGKDKKKKTKKIKEKYIDQEELNKTPIWTRNPDDITQEE
YGEFYKSLTNDWEDHLAVKHFSVEGQLEFRALLFIPRRAPFDLFENKKKKNNIKLYVRRVFIMDSCDELIPEYLN
FIRGVVDSEDLPLNISREMLQQSKILKVIRKNIVKKCLELFSLEAEDKENYKKFYEAFSKNLKLGIHEDSTNRRR
LSELLRYHTSQSGDEMTSLSEYVSRMKETQKSIYYITGESKEQVANS AFVERVRKRGFEVVMTEPIDEYCVQQL
KEFDGKSLVSVTKEGLELPEDEEEKKKMEESKAKFENLCKLMKEILDKKVEKVTISNRLVSSPCCIVTSTYGWTA
NMERIMKAQALRDNSTMGYMAKKHLEINPDHP IVETLRQKAEADKNDKAVKDLVVLLFETALLSSGFSLEDPQT
HSNRIYRMIKLG LGIDED EVA AEEPNA AVPDEIPPLEGDEDASRMEEVD

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FIGURE 5

ATGCAGGCCCCACGGGAGCTCGCGGTGGGCATCGACCTGGGCACCACTACTCGTGCGTGGGCGTGTTCAGCAG
GGCCGCGTGGAGATCCTGGCCAACGACCAGGGCAACCGCACCCAGCTACGTGGCCTTCACCGACACCGAG
CGGCTGGTTCGGGGACGCGGCCAAGAGCCAGGCGGCCCTGAACCCCCACAACACCGTGTTTCGATGCCAAGCGGCTG
ATCGGGCGCAAGTTCGCGGACACCACGGTGCAGTCGGACATGAAGCACTGGCCCTTCGGGGTGGTGAGCGAGGGC
GGCAAGCCCAAGGTGCCGGTATCGTACCGCGGGGAGGACAAGACGTTCTACCCCGAGGAGATCTCGTCCATGGTG
CTGAGCAAGATGAAGGAGACGGCCGAGGCGTACCTGGGCCAGCCCCGTGAAGCACGCAGTGATCACCGTGCCCCGC
TATTTCAATGACTCGCAGCGCCAGGCCACCAAGGACGCGGGGGCCATCGCGGGGCTCAACGTGTTGCGGATCATC
AATGAGCCACGGCAGCTGCCATCGCCTATGGGCTGGACCGGCGGGGCGCGGGAGAGCGCAACGTGCTCATTTTT
GACCTGGGTGGGGGCACCTTCGATGTGTGCGTTCTCTCCATTGACGCTGGTGTCTTTGAGGTGAAAGCCACTGCT
GGAGATACCCACCTGGGAGGAGAGGACTTCGACAACCGGCTCGTGAACCACTTCATGGAAGAATTCCGGCGGAAG
CATGGGAAGGACCTGAGCGGGAACAAGCGTGCCCTCGGCAGGCTGCGCACAGCCTGTGAGCGCGCCAAGCGCACC
CTGTCTCCAGCACCCAGGCCACCCTGGAGATAGACTCCCTGTTTCGAGGGCGTGGACTTCTACACGTCCATCACT
CGTGCCCGCTTTGAGGAACGTGTGCTCAGACCTCTTCCGCAGCACCTGGAGCCGGTGGAGAAGGCCCTGCGGGAT
GCCAAGCTGGACAAGGCCCAGATTTCATGACGTCGTCTGGTGGGGGGCTCCACTCGCATCCCCAAGGTGCAGAAG
TTGCTGCAGGACTTCTTCAACGGCAAGGAGCTGAACAAGAGCATCAACCCTGATGAGGCTGTGGCCTATGGGGCT
GCTGTGCAGGCGGCCGTGTTGATGGGGGACAAATGTGAGAAAGTGCAGGATCTCCTGCTGCTGGATGTGGCTCCC
CTGTCTCTGGGGCTGGAGACAGCAGGTGGGGTGATGACCACGCTGATCCAGAGGAACGCCACTATCCCCACCAAG
CAGACCCAGACTTTCACCACCTACTCGGACAACCAGCCTGGGGTCTTCATCCAGGTGTATGAGGGTGAGAGGGCC
ATGACCAAGGACAACAACCTGCTGGGGCGTTTTGAACTCAGTGGCATCCCTCCTGCCCCACGTGGAGTCCCCCAG
ATAGAGGTGACCTTTGACATTGATGCTAATGGCATCCTGAGCGTGACAGCCACTGACAGGAGCACAGGTAAGGCT
AACAAGATCACCATCACCAATGACAAGGGCCGGCTGAGCAAGGAGGAGGTGGAGAGGATGGTTCATGAAGCCGAG
CAGTACAAGGCTGAGGATGAGGCCCAGAGGGACAGAGTGCGTGCCAAAACTCGCTGGAGGCCCATGTCTTCCAT
GTGAAAGGTTCTTTGCAAGAGGAAAGCCTTAGGGACAAGATCCCCGAAGAGGACAGGCGCAAAATGCAAGACAAG
TGTCGGGAAGTCCTTGCCTGGCTGGAGCACAACCAGCTGGCAGAGAAGGAGGAGTATGAGCATCAGAAGAGGGAG
CTGGAGCAAATCTGTGCCCCATCTTCTCCAGGCTCTATGGGGGGCCTGGTGTCCCTGGGGGCAGCAGTTGTGGC
ACTCAAGCCCCGCCAGGGGGACCCAGCACCGGCCCCATCATTGAGGAGGTTGAT**TGA**

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FIGURE 6

MQAPRELAVGIDLGTTYSCVGVFQQGRVEILANDQGNRTTPSYVAFTDTERLVGDAAKSQAALNPHNTVFDKRL
IGRKFA DTTVQSDMKHWPFRVVS EGGKPKVPVSYRGEDKTFYPEEISSMVL SKMKETA EAYLGQPVKHAVITVPA
YFNDSQRQATKDAGAIAGLNLVRI INEPTAAAIAYGLDRRGAGERNVLIFDLGGGTFDVSVLSIDAGVFEVKATA
GDTHLGGEDFDNRLVNHFMEEFR RKHGKDL SGNKRALGR LR TACERAKRTLSSSTQATLEIDSLFEGVDFYTSIT
RARFEELCSDLFRSTLEPVEKALRDAKLDKAQIHDVVLVGGSTRIPKVQKLLQDFFNGKELNKSINPDEAVAYGA
AVQAAVLMGDKCEKVQDLLLLLDVAPLSLGL ETAGGVMTTLIQRNATIPTKQTQTFTTYS DNQPGVFIQVYEGERA
MTKDNNLLGRFELSGIPPAPRGVPQIEVTFDIDANGILSVTATDRSTGKANKITITNDKGRLSKEEVERMVHEAE
QYKAEDEAQRDRVAAKNSLEAHVFHVKGSLQEESLRDKIPEEDRRKMQDKCREVLAWLEHNQLAEKEEYEHQKRE
LEQICRP IFSRLYGGPGVPGGSSCGTQARQGD PSTGP IIEEVD

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FIGURE 7A

TGCGACCGCCTCCCTGCGCCCCGCCCCTCCGGCTAGCTCGCTGGCTCCCGGCTCCTCCCGACGTCTCCTACCTCC
TCACGGCTCTTCCCCGGCGCTCTCCTGGCTCCCTTCTGCCCCAGCTCCGTCTCGGCGGCGGCGGGCAGTTGCAGTG
GTGCAGAAATGGCTGACCTCAGTCTTGACAGATGCATTAACAGAACCATCTCCAGACATTGAGGGAGAGATAAAGCG
GGACTTCATTGCCACACTAGAGGCAGAGGCCCTTTGATGATGTTGTGGGAGAAAAGTGTGGAAAAACAGACTATAT
TCCTCTCCTGGATGTTGATGAGAAAACCGGGAACCTCAGAGTCAAAGAAGAAAACCGTGCTCAGAAAACCTAGCCAGAT
TGAAGATACTCCATCTTCTAAACCAACACTCCTAGCCAATGGTGGTCATGGAGTAGAAGGGAGCGATACTACAGG
GTCTCCAACCTGAATTCCTTGAAGAGAAAATGGCCTACCAGGAATACCCAAATAGCCAGAACTGGCCAGAAGATAC
CAACTTTTGTTCCTCAACCTGAGCAAGTGGTCGATCCTATCCAGACTGATCCCTTTAAGATGTACCATGATGATGA
CCTGGCAGATTTGGTCTTTCCCTCCAGTGCAGACAGCTGATACTTCAATATTTGCAGGACAAAATGATCCCTTGAA
AGACAGTTACGGTATGTCTCCCTGCAACACAGCTGTTGTACCTCAGGGGTGGTCTGTGGAAGCCTTAAACTCTCC
ACACTCAGAGTCCCTTTGTTTCCCCAGAGGCTGTTGCAGAACCTCCTCAGCCAACGGCAGTTCCCTTAGAGCTAGC
CAAGGAGATAGAAATGGCATCAGAAGAGAGGCCACCAGCACAAAGCATTGGAAATAATGATGGGACTGAAGACTAC
TGACATGGCACCATCTAAAGAAACAGAGATGGCCCTCGCCAAGGACATGGCACTAGCTACAAAAACCGAGGTGGC
ATTGGCTAAAGATATGGAATCACCCACCAATTAGATGTGACACTGGCCAAGGACATGCAGCCATCCATGGAATC
AGATATGGCCCTAGTCAAGGACATGGAATACCCACAGAAAAAGAAGTGGCCCTGGTTAAGGATGTGAGATGGCC
CACAGAAACAGATGTATCTTCAGCCAAGAATGTGGTACTGCCCACAGAAACAGAGGTAGCCCCAGCCAAGGATGT
GACACTGTTGAAAGAAACAGAGAGGGCATCTCCTATAAAAAATGGACTTAGCCCCCTTCCAAGGACATGGGACCACC
CAAAGAAAAACAAGAAAGAAACAGAGAGGGCATCTCCTATAAAAAATGGACTTGGCTCCTTCCAAGGACATGGGACC
ACCCAAAGAAAAACAAGATAGTCCAGCCAAGGATTTGGTATTACTCTCAGAAATAGAGGTGGCACAGGCTAATGA
CATTATATCATCCACAGAAATATCCTCTGCTGAGAAGGTGGCTTTGTCTCAGAAACAGAGGTAGCCCTGGCCAG
GGACATGACACTGCCCCCGGAAACCAACGTGATCTTGACCAAGGATAAAGCACTACCTTTAGAAGCAGAGGTGGC
CCCAGTCAAGGACATGGCTCAACTCCCAGAAACAGAAATAGCCCCGGCCAAGGATGTGGCTCCGTCCACAGTAAA
AGAAGTGGGCTTGTGTAAGGACATGTCTCCACTATCAGAAACAGAAATGGCTCTGGGCAAGGATGTGACTCCACC
TCCAGAAACAGAAGTAGTTCTCATCAAGAACGTATGTCTGCCTCCAGAAATGGAGGTGGCCCTGACTGAGGATCA
GGTCCCAGCCCTCAAACAGAAAGCACCCCTGGCTAAGGATGGGGTTCTGACCCTGGCCAACAATGTGACTCCAGC
CAAAGATGTTCCACCCTCTCAGAAACAGAGGCAACACCAGTTCCAATTAAAGACATGGAAATTGCACAAAACACA
AAAAGGAATAAGTGAAGATTCCCATTAGAAATCTCTGCAGGATGTGGGGCAGTCAGCTGCACCTACTTTTCATGAT
TTCACCAGAAACCATCACAGGAACGGGGAAAAAGTGCAGCTTGCCGGCCGAGGAGGATTCTGTGTTAGAAAAACT
AGGGGAAAGGAAACCATGCAACAGTCAACCTTCTGAGCTTCTTCAGAGACCTCAGGAATAGCCAGGCCAGAAGA
AGGAAGGCCTGTGGTGAGTGGGACAGGAAATGACATCACCAACCCACCGAACAAGGAGCTCCACCAAGCCCAGA
GAAGAAAAACAAGCCTTTGGCCACCCTCAACCTGCAAAGACTTCAACATCGAAAGCCAAAACACAGCCCACTTC
TCTCCCTAAGCAGCCAGCTCCCACCACCATTTGGTGGGTGAAATAAAAAACCATGAGCCTTGCTTCAGGCTTAGT
GCCAGCTGCCCCACCCAAACGCCCTGCCGTGCCTCTGCCAGGCCTTCCATCTTACCTTCAAAGACGTGAAGCC
AAAGCCCATTCAGATGCAAAGGCTCCTGAGAAGCGGGCCTCACCATCCAAGCCAGCTTCTGCCCCAGCCTCCAG
ATCTGGGTCCAAGAGCACTCAGACTGTTGCAAAAACACAACAGCTGCTGCTGTTGCCTCAACTGGCCCAAGCAG
TAGGAGCCCCCTCCAGCTCCTGCCCAAGAAGCCCACTGCCATTAAGACTGAGGGAAAACCTGCAGAAGTCAAGAA
GATGACTGCAAAGTCTGTACCAGCTGACTTGAGTCGCCCCAAAGAGCACCTCCACCAGTTCCATGAAGAAAACCA
CACTCTCAGTGGGACAGCCCCGCTGCAGGGGTGGTTCCAGCCGAGTCAAGGCCACACCCATGCCCTCCCGGCC
CTCCACAACCTCCTTTTCATAGACAAGAAGCCCACTCGGCCAAACCCAGCTCCACCACCCCCGGCTCAGCCGCT
GGCCACCAATACTTCTGCTCCTGATCTGAAGAATGTCCGCTCCAAGGTTGGCTCCACGGAAAAACATCAAGCATCA
GCCTGGAGGAGGCCGGGCCAAAGTAGAGAAAAAAACAGAGGCAGCTGCTACAACCCGAAAGCCTGAATCTAATGC
AGTCACTAAAACAGCCGGCCCAATTGCAAGTGCACAGAAAACAACCTGCGGGGAAAGTCCAGATAGTCTCCAAAAA
AGTGAGCTACAGCCATATTCAGTCCAAGTGTGGTTCCAAGGACAATATTAAGCATGTCCCTGGAGGTGGTAATGT
TCAGATTGAGAAACAAGAAAGTGGACATCTCTAAGGTCTCCTCCAAGTGTGGGTCTAAGGCTAACATCAAGCACAA
GCCTGGTGGAGGAGATGTCAAGATTGAAAGTCAGAAGTTGAACCTCAAGGAGAAGGCCAGGCCAAGGTGGGATC
CCTCGATAATGTGGGCCACCTACCTGCAGGAGGTGCTGTGAAGACTGAGGGCGGTGGCAGCGAGGCTCCTCTGTG
TCCGGGTCCCCCTGCTGGGGAGGAGCCGGCCATCTCTGAGGCAGCGCTGAAGCTGGCGCCCCCACTTCAGCCAG
TGGCCTCAATGGCCACCCCAACCTGTGAGGGGTGGTGACCAAGGGAGGCCAGACCTTGACAGCCAGATCCA

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FIGURE 7B

GGAGACAAGCATCTAAATGATGACATTCTGGTCTCGTCTTCCGTCTCCCCCGTGTTCCCCTCTTGTCTCCCCTGTT
CCCCTCTCCCTTCCCTCCTCCCATGTCACTGCAGATTGAGACCTACAGGCTGACGTTCCGGGCAAATGCCAGGGC
CCGCACCGACCACGGGGCCGACATTGICTCCCGCCCCCACAATTCCCTGGCGGGCCCAACTCGGGCTCCCGGGT
CCTTGGCCCCCTTTCCCGGGCTGTCCACTAGACCAGTGAGCGCTTGGGCGCCGTGCTGGGCAGCCCGCTAGGCTC
GCCTTCCCCTCCTGCTTTGCGTGCCCGGGGCAGCAGCAGCCCTGCCCCACACCTCCTCTCACTCCCCAGCCTGGGC
CCATCTCCCTGCTTTGGTCTTGCCCCATCACTGCGCCACTGCTCCGTGGAGGAGGTTGGGAGGGGGTTGGGGTGG
TTGAGGCTAAGTTGGGATCTAGGAGAGGAGAACCAGATTCTATCCTCATCTTTTTTTGGTTCTTTGGTCCAAACC
CAAAAGAACTGACATGCCCTCCCTTCTCCCTGGATCTACCTGGAGGGAAGAGTGGAGGTGGATTCCGAGTGGTG
ACAGGACGCTGACCGTGGAGCTTAAGCCACTGCCTCTCCCTCTGGTCCCACAAATGGGCGCCCCCCCCCTCCCCAT
GCAGGTGGTGTGCGGGCCCTTCTTGCTGCCCTGCCCCAAGTTGGGGGTCAGTGCTGCCTGTCCCCATGCTTAACAT
ACCCGCCTAGCTGCTGTACATTTTTCTTGTTTTGTCTTTTATTTTTTTCTAATAACCTAAAAACTGGCAAAAT
AGTTCTGCAGGTGAAGCCATGTCTACATGAAAGTCCTCAGTAAGTGTTAGAGGGAACAGGGCGGAGATATCCTT
ATGCCACCCCGCTGGAGGATGTGGGCAGCTTAGGGCCCTGGAGGCGGTGCGGCAGGGAAGAGGGGTGCAGAGGC
TGTGGCTGGTGAGCCGGTCAGGCACACAAGGGGCCCTTGGAGCGTGGAAGTGGTTGGTTTTGCCATTTTGTGTGT
GTATGCTGCTTTTCTTTTCTAACCAAGAGGCTGGTTTTGGCATCTCTGTCCCATTCCCTGGGATCTGGTGGTCAG
CCCTAGGATAAAAAGCCAGGGCTGGAGAACAAGAAAGGGCCAGGAGATGAATTC

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FIGURE 8

MADLSLADALTEPSDIEGEIKRDFIATLEAEAFDDVVGETVGKTDYIPLLDVDEKTGNSESKKKPCSETSQIED
TPSSKPTLLANGGHGVEGSDTTGSPTEFLEEKMAYQEYPNSQNWPEDTNFCFQPEQVVDPIQTDPFKMYHDDDLA
DLVFPSSATADTSIFAGQNDPLKDSYGMSPCNTAVVPQGWSVEALNSPHSESFVSPEAVAEPPOPTAVPLELAKE
IEMASEERPPAQALEIMMGLKTTDMAPSKETEMALAKDMALATKTEVALAKDMESPTKLDVTLAKDMQPSMESDM
ALVKDMELPTEKEVALVKDVRWPTETDVSSAKNVVLPTETEVAPAKDVTLKETERASPIKMDLAPSKDMGPPKE
NKKETERASPIKMDLAPSKDMGPPKENKIVPAKDLVLLSEIEVAQANDIISSTEISSAEKVALSSETEVALARDM
TLPPETNVILTKDKALPLEAEVAPVKDMAQLPETEIAPAKDVAPSTVKEVGLLKDMSPILSETEMALGKDVTPPPE
TEVVLIKNVCLPPEMEVALTEDQVPALKTEAPLAKDGVLTLANNVTPAKDVPPLSETEATPVPIKDMEIAQTQKG
ISEDHLESLODVGQSAAPTTFMISPETITGTGKKCSLPAEEDSVLEKLGERKPCNSQPSSELSSETSGIARPEEGR
PVVSGTGNDITTPPNKELPPSPEKKTPLATTQPAKTSTSKAKTQPTSLPKQPAPTTIGGLNKKPMSLASGLVPA
APPKRPAVASARPSILPSKDVKPKPIADAKAPEKRASPSKPASAPASRSGSKSTQTVAKTTTAAAVASTGPSSRS
PSTLLPKKPTAIKTEGKPAEVKKMTAKSVPADLSRPKSTSTSSMKKTTTSLGTAPAAGVVP SRVKATPMP SRPST
TPFIDKKPTSAPKSSTTPRLSRLATNTSAPDLKNVRSKVGSTENIKHQPGGGRKVEKKTEAAATTRKPESNAVT
KTAGPIASAQKQPAGKVQIVSKKVSYSHIQSKCGSKDNIKHVPGGGNVQIQNKKVDISKVSSKCGSKANIKHKPG
GGDVKIESQKLNFKKAQAKVGSLDNVGHLPAGGAVKTEGGGSEAPLCPGPPAGEEPAISEAAPEAGAPTSASGL
NGHPTLSGGGDQREAQTLDSQIQETSI

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FIGURE 9

CCGGCACGAGAGGAGTTGTGAGTTTCCAAGCCCCAGCTCACTCTGACCACTTCTCTGCCTGCCCAGCATCATGAA
GGGCCTTGCAGCTGCCCTCCTTGTCTCGTCTGCACCATGGCCCTCTGCTCCTGTGCACAAGTTGGTACCAACAA
AGAGCTCTGCTGCCTCGTCTATACCTCCTGGCAGATTCCACAAAAGTTCATAGTTGACTATTCTGAAACCAGCCC
CCAGTGCCCCAAGCCAGGTGTCATCCTCCTAACCAAGAGAGGCCGGCAGATCTGTGCTGACCCCAATAAGAAGTG
GGTCCAGAAATACATCAGCGACCTGAAGCTGAATGCCTGAGGGGCCTTGGGAAGCTGCGAGGGCCCAGTGAACCTGG
TGGGCCCAGGAGGGAACAGGAGCCTGAGCCAGGGCAATGGCCCTGCCACCCCTGGAGGCCACCTCTTCTAAGAGTC
CCATCTGCTATGCCCAGCCACATTAACCTAATCTTAGTTTATGCATCATATTTTCAATTTTGAATTGATTT
CTATTGTTGAGCTGCATTATGAAATTAGTATTTTCTCTGACATCTCATGACATTGTCTTTATCATCCTTTCCCT
TTCCCTTCAACTCTTCGTACATTCAATGCATGGATCAATCAGTGTGATTAGCTTTCTCAGCAGACATTGTGCCAT
ATGTATCAAATGACAAATCTTTATTGAATGGTTTTGCTCAGCACCACTTTTAATATATTGGCAGTACTTATTAT
ATAAAAGGTAAACCAGCATTCTCACTGTGAAAAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 10

MKGLAAALLVLVCTMALCSCAQVGTNKELCCLVYTSWQIPQKFIVDYSETSPQCPKPGVILLTKRGRQICADPNK
KWVQKYISDLKLNA

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FIGURE 11

ATTCCGCTCTTGCTTTCCGGCAGGTGATGGCGCCCCCGCGGCCTAGAGGTCCAGCGCCCCGCGGAGCAGCGGA
CAGTCCTCCTGTTGTGTCCGACCGAGAGTCCTGGTGACTTTGAACATGCTGGTGCCGCTAGCCAAGCTGTCCTGC
CTGGCATATCAGTGCTTTTCATGCCTTAAAAATTAAGAAAAATTATCTACCTCTATGTGCTATAAGATGGTCTTCA
ACTTCTACTGTGCCCTCGAATTACTACCCATTATACTATTTATCCCCGGGATAAGGACAAGAGATGGGAAGGAGTG
AACATGGAAAGGTTTGCAGAAGAAGCAGATGTTGTAATAGTTGGTGCAGGCCCTGCAGGGCTCTCTGCAGCTGTT
CGTCTAAAACAGTTGGCTGTGGCACATGAAAAGGACATCCGTGTGTGTCTAGTGGAGAAAGCTGCCCAGATAGGA
GCTCATACTCTCTCAGGGGCTTGCCTTGATCCAGGTGCTTTTAAAGAACTCTTCCCAGACTGGAAAGAGAAGGGG
GCTCCACTTAACACTCCTGTAACAGAAGACAGATTTGGAATTTTAACAGAGAAATACAGAATTCCTGTGCCAATT
CTTCCAGGGCTTCCAATGAATAATCATGGCAATTACATTGTACGCTTGGGACATTTAGTGAGCTGGATGGGCGAA
CAAGCAGAAGCCCTTGGTGTGAAGTATACCCTGGTTATGCAGCTGCTGAGGTCCTTTTTTCATGATGATGGTAGT
GTAAAGGAATTGCCACTAACGATGTAGGGATACAAAAGGATGGTGCACCAAAGGCAACATTTGAGAGAGGACTG
GAACTACATGCTAAAGTCACAATTTTGCAGAAGGTTGCCATGGACATCTAGCCAAGCAACTATATAAGAAGTTT
GATTTGAGAGCAAAATTGTGAACCTCAAACCTACGGGATTGGACTGAAGGAGTTATGGGTTATTGATGAAAAGAAC
TGGAACCTGGGAGAGTAGATCACACTGTTGGTTGGCCCTTGGACAGACATACCTATGGAGGATCTTTCCTCTAT
CATTTGAATGAAGGTGAACCCCTAGTAGCTCTTGGTCTTGTGGTTGGTCTAGACTATCAGAATCCATACCTGAGT
CCATTTAGAGAGTTCCAAAGGTGGAACACCATCCTAGCATTTCGGCCAACCTTGGAAGGTGAAAAAGGATTGCA
TACGGAGCCAGAGCTCTCAATGAAGGTGGCTTTTCAGTCTATACCAAACTCACCTTTCCTGGTGGTTTACTAATT
GGTTGTAGTCCTGGTTTTATGAATGTTCCCAAGATCAAAGGTACTCACACAGCAATGAAAAGTGGAATTTTAGCA
GCAGAATCTATTTTAACTAATACTAGTGAAAATCTCCAATCAAAGACAATAGGACTCCATGTAAGTGAATAT
GAGGACAATTTGAAGAACTCATGGGTATGGAAAGAGCTATATTCTGTTAGAAATATAAGACCGTCTGCCACGGA
GTACTGGGTGTATATGGAGGGATGATTTACACTGGAATCTTTTACTGGATATTGAGAGGAATGGAGCCGTGGACT
CTGAAACATAAAGGTTCTGACTTTGAACGGCTCAAGCCAGCCAAGGATTGCACACCTATTGAGTATCCAAAACCC
GATGGACAGATCAGTTTTGACCTCTTGTCTCTGTGGCTCTGAGTGGTACTAATCATGAACATGACCAGCCGGCA
CACTTAACCTTAAGGGATGACAGTATACCTGTAAATAGAAAATCTGTCGATATATGATGGGCCCCGAGCAGCGATT
TGTCTGCAGGAGTTTATGAATTTGTACCTGTGGAACAAGGTGATGGATTTTCGGTTACAGATAAATGCTCAGAAC
TGTGTACATTGTAAAACATGTGATATTAAAGATCCAAGTCAGAATATTAACTGGGTGGTACCTGAAGGTGGAGGA
GGACCTGCTTACAATGGAATGTAAACTGCAGCTAGCCAGTTTCTTTCAAGTATGGCAAGCTAACGTTAAAATGTT
TAGAGATTAACAGATTTTCAAGATGTCTTCTGCATATTACTGAACAGAATAGTCACAAAATGATTATCAAATAAA
AATTTTATACTATAAAAAAAAAA

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FIGURE 12

MLVPLAKLSCLAYQCFHALKIKKNYLPLCAIRWSSTSTVPRITTHYTIYPRDKDKRWEGVNMERFAEEADVIVG
AGPAGLSAAVRLKQLAVAHEKDIRVCLVEKAAQIGAHTLSGACLDPGAFKELFPDWKEKGAPLNTPVTEDRFGIL
TEKYRIPVPILPGLPMNNHGNYIVRLGHLVSWMGEQAEALGVEVYPGYAAAEVLFHDDGSVKGIATNDVGIQKDG
APKATFERGLELHAKVTIFAEGCHGHLAKQLYKKFDLRANCEPQTYGIGLWVIDEKNWKPGRVDHTVGWPLD
RHTYGGSFYHLNEGEPLVALGLVVGGLDYQNPYLSPPREFQRWKHHPSIRPTLEGGKRIAYGARALNEGGFQSIP
KLTFPGLLIGCSPGFMNVPKIKGTHAMKSGILAAESIFNQLTSENLSKTIGLVTEYEDNLKNSWVKELYS
VRNIRPSCHGVLGVYGGMIYTGIFYWILRGMEPWTLLKHKGSDFERLKPDKCTPIEYKPDGQISFDLLSSVALS
GTNHEHDQPAHLTLRDDSIPVNRNLSIYDGPEQRFCPAGVYEFVPVEQGDGFRQINAQNCVHCKTCDIKDPSQN
INWVVPEGGGGPAYNGM

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FIGURE 13

CTCAGCTTCTTTGCGTAACCAATACTGGAAGGCATTTAAAGGACCTCTGCCGCCTCAGACCTTGCAGTTAACTCC
GCCCTGACCCACCCCTTCCCGATGCAGTCCCTGATGCAGGCTCCCCCTCCTGATCGCCCTGGGCTTGCTTCTCGCGA
CCCCTGCGCAAGCCACCTGAAAAAGCCATCCCAGCTCAGTAGCTTTTCTGGGATAACTGTGATGAAGGGAAGG
ACCCTGCGGTGATCAGAAGCCTGACTCTGGAGCCTGACCCCATCGTCGTTCTGGAAATGTGACCCTCAGTGTGCG
TGGGCAGCACCAGTGTCCCCCTGAGTTCTCCTCTGAAGGTGGATTTAGTTTTGGAGAAGGAGGTGGCTGGCCTCT
GGATCAAGATCCCATGCACAGACTACATTGGCAGCTGTACCTTTGAACACTTCTGTGATGTGCTTGACATGTTAA
TTCCTACTGGGGAGCCCTGCCAGAGCCCTGCGTACCTATGGGCTTCCTTGCCACTGTCCCTTCAAAGAAGGAA
CCTACTCACTGCCCCAAGAGCGAATTCGTTGTGCCTGACCTGGAGCTGCCAGTTGGCTCACCACCGGGAACCTACC
GCATAGAGAGCGTCTGAGCAGCAGTGGGAAGCGTCTGGGCTGCATCAAGATCGCTGCCTCTCTAAAGGGCATAT
AGCATGGCATCTGCCACAGCAGAATGGAGCGGTGTGAGGAAGGTCCCTTTTCTCTGTTTTGTGTTTGCCAAGGC
CAAACCTCCACTCTCTGCCCCCTTTAATCCCTTTTCTACAGTGAGTCCACTACCCTCACTGAAAATCATTTTGT
ACCATTACATTTTAGGCTGGGGCAAGCAGCCCTGACCTAAGGGAGAATGAGTTGGACAGTTCTTGATAGCCAG
GGCATCTGCTGGGCTGACCACGTTACTCATCCCCGTTAACATTCTCTCTAAAGAGCCTCGTTCATTTCCAAAGCA
GTTAAGGAATGGGAACAGAGTGTTTTAGGACCTGAAGAATCTTTATGACTCTCTCTCTTTCTCTCTTTTTTTTTT
TGTCATAAGTTAAAAAGCGAAGTGAGAGTATTAACGTTTTTGTCTCCTCCGGCCCCCTGTTACAATGAAGGGGC
AAAAGTATTTGCTCTTAGTCTATTCCTCCCTTAACTTCTGTGACTAATTTTTATTTCCTTTCTAGATTTGCCAA
TTAATACTAGGGTGCAGTGTATCCTGGAGAGGTAGGGTGTGTGGGGGAGGAATCCCTTGGGGGAGATATTAGGAG
TGCTCTGTTGTTTACAACTCAGGTACCCGCAGGGCCTAGCAAGAGACTTAAATGACTGATAAGAACCCTGAGAA
ACATGTTGCTTCCAGGCTTGATTTTCGATTTTTTCGCTTTTTTTTTTTTGGGACGGAGTCTCGCTTTGTACCAGGCT
GGAGTGCAGTGGTGCAATCTCACCTCACTGCAACCTCCGCCTCCTGGGTTCAAGCAATTCTCCTGCCTCAGCCTC
CCAAGTAGCTTGGACTACAGGCCCTGCCACCACGCCC GGCTAATTTGTGTATTTTAGTAGAGATGGGGTTTTCAC
CATGTTGGCCAGGATGGTCTCGATCTCTTGACCTCGTGATCCGTCCACCTTGGCCTTGCAAAGCGCTGGATTACA
GGCATGAGCCACTACACCCAGCCGATTTTTCTTTTTTGATTAAAGATGCTATTACAATGTAAATATTTCTTACAC
AGAAAGTCACAGCACATGTGCCATTGATACAAGGCTGCTGAGGCCTGGTCTCCAGTTGGAAATATAATTAAGGG
TGGCAGGGACTGGAGTCAGTTGGAGAGTGCATAGCCAGTCTGTGAAGACAACCTGCCAGATACTGGCAATACTCCA
GCCTGGTGACAGAGTGAGACTCTGTCTCAAAAAAAAAAGTTTCAATGTTTACTCCTAGAGAAGCCAAAAATCCAGA
TTTGTATATGAAATCTTACCATTTTAAAAGATTGGCAGCTAATTATTTTTTTAAAAGCTGTGCAGTGTGATGTG
TCCCAAACGGACTGGCTCATGGGTGGCCACGTCACAACCTCTGATCTCAGACCGTGCATGCCTTGTCTCTTAAG
ACAACTCCTGTGGCACCGTTTCTCCCTCCACAGGGCCAAAGCCATAGTGTCGGGTCCCAAGGACAAGGCTCTTCC
AGTGCTAGGAGAGGTATGAGCAGCCTCTCACCTGTGAGCTGTGGGGATCACAAGGCTGCCTGCCTCAGTCTTGGA
GTCCTGTTGGGTGAATGAGGCAGATGGGAAAGAGCCTCACCAGCAGCTGCTTTTGGAGCAGGGGTCCAAGGAAGA
GAGGGTGGCCTCGACATCAAACCTGCCTGGATTTTCTACCACCTGTTACATCATAACAACCTTCTGAAACACACA
CCAGCCCTGAGTTCTGGGCTCATTTGAAGCCTGGAATAGCAATAAATCTTTTAACTTGCAAAAAAAAAAAAAAAA
AAA

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FIGURE 14

MQSLMQAPLLIALGLLLATPAQAHLKKPSQLSSFSWDCDEGKDPVIRSLTLEPDPIVVPGNVTLVVGSTSV
LSSPLKVDLVLEKEVAGLWIKIPCTDYIGSCTFEHFCDVLDMLIPTGEPCPEPLRTYGLPCHCPFKEGTYS
LPKS
EFVVPDLELPSWLTGNYRIESVLSSSGKRLGCIKIAASLKGI

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FIGURE 15

GAAAGATGGCGTCTCTCGGAGCAGGCAGAGCAGCCGAGCCAGCCAAGCTCTACTCCAGGAAGTGAAAATGTGCTGC
CTCGAGAGCCGCTGATTGCCACGGCAGTGAAGTTTCTACAGAATTCCCGGGTCCGCCAGAGCCCACTTGCAACCA
GGAGAGCATTTCATAAGAAGAAAGGGCTGACAGATGAAGAGATTGATATGGCCTTCCAGCAGTCGGGCACTGCTG
CCGATGAGCCTTCGTCTTGGGCCCAGCCACACAGGTGGTTCCCTGTCCAGCCCCCTCACCTCATATCTCAGCCAT
ACAGTCCCGCAGGCTCCCGATGGCGAGATTACGGCGCCCTGGCCATCATCATGGCAGGCATTGCATTTGGCTTTC
ACCAGCTCTACAAGAAATACCTGCTCCCCCTCATCCTGGGCGGCCGAGAGGACAGAAAGCAGCTGGAGAGGATGG
AGGCCGGTCTCTCTGAGCTGAGTGGCAGCGTGGCCCAGACAGTGAAGTACAGACGACCCTCGCCTCCGTCC
AGGAGCTGCTGATTCAGCAGCAGCAGAAGATCCAGGAGCTTGCCCCAGAGCTGGCCGCTGCCAAGGCCACCACAT
CCACCAACTGGATCCTGGAGTCCCAGAATATCAACGAACTCAAGTCCGAAATTAAGTCCCTTGAAAGGGCTTCTTT
TAAATCGGAGGCAGTTCCTCCATCCCCATCAGCCCCGAAGATCCCCCTGTCAGATCCCAGTCAAGTCACCGT
CACCTCCAGCCCTGCGGCCGTGAACCACCACAGCAGCAGCGACATCTCACCTGTCAGCAACGAGTCCACGTCGT
CCTCGCCTGGGAAGGAGGGCCACAGCCCCGAGGGCTCCACGGTCACCTACCACTTGCTGGGCCCCCAGGAGGAAG
GCGAGGGGGTGGTGGACGTCAAGGGCCAGGTGCGGATGGAGGTGCAAGGCGAGGAGGAGAAGAGGGAGGACAAGG
AGGACGAGGAGGATGAGGAGGATGATGATGTGAGCCATGTGGACGAGGAGGACTGCCTGGGGGTGCAGAGGGAGG
ACCGCCGGGGCGGGGATGGGCAGATCAACGAGCAGGTGGAGAAGCTGCGGCGGCCCGAGGGGCCAGCAACGAGA
GTGAGCGGGACTAGGGCTGCGCCTGCTGCCTCCAGCCCTGAGGATGGCATCTAGTGTGCCCGTGCCTGGCCATAC
CCTGCCTCCCTCTCTGGCCCTGGGAGGGCAGCTTGGAGCCCAGGTAGGGGGCAGAGCTGTCCTCAGCTGCACTGC
GGCCTGGTGGCAGTGTGGGGAGTCACACTTCTGTCCACCTGGCCTCCTCTCGCCTGGCCGCCAGCCCCAGCCCCA
GCCCCAGCCCCAGGCCAGCTGCCTTTGGCTTTGATCTCAAGTCAGGCTGAAGGCAGCGAAGCCTCGGGGGCCAA
GCCCCCTCCCCAGCCCCCTCTCCCGACAGACGCCTTGCCCAGGGTGTGTTTGCTGAGTGTCTTGACTACCGTGAC
ACCACGCATGGCCAGAGCTAGCGTCCCTACTGCCTCCCGACTCCTCAGTGGAGGAGGAGCTGCGGTCCCTCTGGT
GTCTGCCATCCCCCTCCCTCCCTGGGCCCGGCCCTGGACCCGTCAGGTGCCTGTCCCCAGCCCCAACCCCACTCA
TGCCCCGTCGTCTCCAGACAAATGAAACCACGCTGCGCTTCCGATGCCCCGCTTGCCGTGTAATGGTTTCAGC
TAATCCCATGGCGAGATGGGGGCTCATTCCGGAGGAGGAGCCAGGCAGCAGGGCCTTCCTGACCAACAGCCAGTT
TTGTCTTCCCCCAGGAAAAAATGTTTATTGTGTGATCATGTATAGACCTCAGAACGGAAGATAGGACTGTA
TATAATTGTAATAAATACCAGTTGCCACTATTT

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FIGURE 16

MASSEQAEQPSQPSSTPGSENVLPREPLIATAVKFLQNSRVRSPLATRRRAFLKKKGLTDEEIDMAFQQSGTAAD
EPSSLGPATQVVPVQPPHLISQPYSPAGSRWRDYGALAIIMAGIAFGFHQLYKKYLLPLILGGREDRKQLERMEA
GLSELSGSVAQTVTQLQTTLASVQELLIQQQKIQELAHELAAAKATTSTNWILESQNINELKSEINSLKGLLLN
RRQFPSPSPAPKIPSWQIPVKSPSPSSPAAVNHSSSDISPVSNESTSSSPGKEGHSPEGSTVTYHLLGPEEGE
GVVDVKGQVRMEVQGEEKREDKEDEEDEEDDDVSHVDEEDCLGVQREDRRGGDGQINEQVEKLRRPEGASNESE
RD

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FIGURE 17A

GCTGTTTTGACAACATGGCGGCGCCCATGGTCCGTGGCCCGGCAGTGCTCGCCTAAAGGTGGAGAACGAGGAGTA
GAGGAGGCCGAGCCAGAGCCTGTGAGCAGATCCAGACCTACAGATAAAAAACATTATTTAATCTATCTGGGATT
TACTCCGGCTTATGATTTGAGGGCCTTCTCACCTTCTGAAGAATGGCCTTCTGTTTGGCAGAGATTGGGTTTTTAT
GCCTCTCTTCTGAAAAGACAGCTAAATGGTGGGCCAGATGTCTATCAAGTGGGAAAGGAGAGTAATTCCTCGGATGT
ACCAGAAGCATCTACAGTGCCACGGGAAAGTGGACAAAAGAGTATACATTGCAGACAAGAAAGGATGTTGAGAAA
TGGTGGCATCAACGAATAAAAGAACAGGCCTCCAAAATTTTTCAGAAAGCTGATAAATCGAAGCCAAAATTTTACGTG
CTTTCCATGTTCCCTTATCCTTCTGGTAAGCTGCACATGGGCCATGTGCGTGTCTACACCATCAGCGACACCATA
GCACGGTTCCAGAAGATGAGAGGGATGCAGGTCATCAACCCCATGGGATGGGATGCTTTTGGATTGCCTGCTGAA
AATGCCGCAGTCGAGAGGAATCTACATCCACAAAGTTGGACACAAAGTAATATTAAACACATGAGGAAACAGCTT
GATCGTCTGGGCCTGTGTTTTCAGCTGGGATAGGGAAATAACTACGTGTTTGCCAGATTACTACAAGTGGACTCAG
TATCTCTTTATTAACTGTATGAGGCTGGGCTGGCCTATCAAAAGGAGGCCCTGGTTAACTGGGACCCAGTGGAT
CAAACAGTGCTTGCCAATGAGCAGGTGGATGAACATGGCTGTTCATGGCGTTCTGGAGCAAAGGTGGAACAGAAG
TACCTCAGACAATGGTTTATTAAAGACAACCGCTTATGCAAAGGCCATGCAGGACGCGTTGGCAGACCTTCCAGAA
TGGTATGGAATAAAAGGCATGCAAGCCCACTGGATTGGGGACTGTGTGGGCTGCCACCTGGACTTCACATTAAAG
GTTTCATGGGCAAGCCACGGGCGAAAAGCTGACTGCCTATACGGCCACCCCTGAAGCCATTTATGGCACCTCCAC
GTGGCCATCTCGCCAGCCACAGACTCCTACATGGGCACAGCTCTCTGAAGGAAGCCTTGAGGATGGCCCTTGTC
CCTGGCAAAGATTGCCTCACGCCTGTAATGGCTGTGAACATGCTTACCCAGCAGGAGGTCCCTGTCGTTATTTTG
GCCAAAGCTGACTTGGAAGGCTCTCTGGATTCAA⁷AAATAGGAATTCCCAGTACTAGCTCAGAGGACACCATCTTA
GCCCAAACCTTGGGCCTGGCCTACTCTGAAGTCATTGAAACTTTGCCAGATGGCACAGAGAGACTGAGCAGCTCT
GCTGAGTTACAGGTATGACCCGGCAGGATGCTTTTCTAGCCCTGACTCAGAAAGCCCGGGGGAAGAGAGTGGGT
GGAGACGTGACAAGTGATAAACTGAAAGACTGGCTGATTTTACGGCAGCGGTACTGGGGCACACCAATCCCCATT
GTCCACTGCCAGTCTGTGGCCCCACACCTGTGCCCTTGAGGACTTGCTGTGACCCTGCCCAACATCGCGTCT
TTCACTGGCAAGGGAGGCCCCCCACTGGCCATGGCTTCAGAGTGGGTGAACGCTCCTGCCCAAGGTGCAAGGGA
GCAGCCAAGAGAGAGACAGACACGATGGATACCTTTGTTGATTCTGCTTGGTACTACTTCAGATACACTGACCTT
CATAATCCACACAGCCCTTTTAAACACAGCAGTGGCCGATTACTGGATGCCTGTGGATTGTGACATTGGAGGGAAA
GAACATGCCGTTCATGCACCTTGTCTATGCAAGATTCTTTAGTCATTTTGGCATGATCAAAAAATGGTTAAACAT
AGGGAGCCTTTTCATAAGCTGCTGGCCCAAGGCCTTATCAAGGGGCAGACATTCCGCCTACCATCTGGACAGTAT
CTACAGAGAGAGGAAGTGGATCTCACAGGTTCCGTTCTGTTCATGCAAAAACGAAAGAGAAGTTAGAGGTGACG
TGGGAGAAGATGAGTAAGTCCAAACACAACGGGGTGGACCCAGAGGAAGTTGTGGAGCAGTATGGGATCGACACG
ATTCCGGCTCTACATCCTTTTGTGCCCCCTCCTGAGAAGGATATCTTGTGGGATGTGAAAACATGATGCTCTCCCT
GGGGTGCTGAGATGGCAACAACGACTGTGGACCTTGACAACTCGGTTTATTGAGGCCAGGGCTTCTGGGAAGTCT
CCCCAGCCTCAGCTGCTGAGTAACAAGGAGAAAGCTGAGGCCAGGAAGCTCTGGGAGTACAAGAACTCCGTCATC
TCTCAGGTGACCACCCATTTACAGAGGACTTCTCACTGAATTCTGCAATTTCTCAGCTGATGGGACTCAGCAAT
GCCCTCTCGCAAGCCTCTCAGAGCGTCATTCTCCACAGCCCCGAGTTTGAGGATGCTTTGTGTGCCCTGATGGTA
ATGGCTGCTCCACTGGCCCCCTCATGTAACCTCAGAGATCTGGGCAGGCCTGGCGCTGGTGCCGAGGAAGCTCTGT
GCCCACTACACTTGGGATGCCAGTGTGCTGCTCCAGGCATGGCCTGCTGTGGACCCGGAGTTCTGCAGCAGCCT
GAGGTTGTCCAGATGGCAGTTCTGATCAACAATAAAGCTTGTGGCAAATTCCTGTGCCCAACAAGTTGCCCGG
GACCAGGACAAAGTCCACGAATTTGTTCTTCAAAGCGAGCTGGGTGTCAGGCTTTTGCAAGGACGAAGCATCAAG
AAGTCCTTCCTTTCCCGAGAAGTGCCTCATCAACTTCCTGGTGCAAGATTGACAGCCAGGAGGCTGCAGCTAC
CACGAGGGCCTCTGAGGAACCTCCTTCCAGGCCTGGGATGAGGGGGCGATGTCTGCTGGCCCAGGGGAAGGGAAA
AGACAAATGTCTTGACTGTTGACCTCGGTCCTGTGGCAGACTGCAGTCAACAGTGTGCCTCTGTAGTGTGGCCTG
GTGCTGGGGTGAAGGTGAGCTGGGCAAAGGAGAAATATGAGCTACTGAGGAGGGGGTTGGACATCCTGCCCTCA
CCCCCACCCACACTGCAGGTAGAGGAGGCCATCTGATCCCATGGGAAGCCATCAGAGACACTGCTGGTGGGAGC
AGGAAGGAGCAGTGCCCCCTCGAGCAGCCAGGAAGCCTGCGGATCTGGGAAATGGCTCTGCCTTAGGCACCTTCTCG
GGAATTTGAGGCCAGCCTGAGGAAGTGCAGGACTCAGGTGCAATGTGCCAGCCACTTGGAAGTCTAACTGAGCC
TCCAGATGGTAGTGAATGGTCTCTTTGCCTTCAGGCTGGATGAGGAAGTCATTTAGGAAATGTTCAAATAACCAA
TATGTGGAATGGACACAGGGATCTTCTGAAGTTGCTTTGAATCAAAGGCAGGCAGTGTGGTTTCTCTGCCTG
TGTCCCCACCACTCCCCAGCTCTGTCTATGCAGGCCTGTCTCCCCAACCCAGCTGGATGTGCCTCCCAGGCCTG

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FIGURE 17B

CTGTGGTTCTGACACACAGGATCCCAGGCAAGGCACCACTTCCTCACATGAATGAGGAGCAGCAAGTCATAACCA
CTCCCTTGGGTATACAATTTGCTGTGTAGTGAAGTGGAACCAGGCTCAGGCTGCTGGTCCCAACCTCAGAGCCCC
ACCGCAGCCCAGTAGGGATGCAGCACGCCCCAGAGGGCTCATGTGGGCCCCAGATGGCAATGCCACCATTGTTGA
TGTGACTCCAGAGCCAGTTATTAGGAAGAGCAAGCTCACCACAGAGGAGTGGAAGTGGGCCCCCAGATGTTGC
CTCCGGTGTCCAAGCCACAGCGGTCTGGCTGTTGGGAAGATGGCCAGGAATGGACTCATACCATTGGCACATTAG
GCTAATCCTGGTTTTATGTGAAGTCAGCAATTAAGTGTTCCCACTAGAACTGACCTAAGCCACTGATTAATATTT
AATGAGGGAAGGTAGGGGAGAATCTAGCCATTTTATAATGCCAGAAATCTATATATGTTATCTGATGCCATTTTT
CTGAAGTAGCCTCACATGTGGTCCCCCTGCAGTTCAGCAGTTAACAGATGACTTTTTTAGTGTAAATAAAATGTTT
ATCATCTATG

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FIGURE 18

MASVWQRLGFYASLLKRQLNGGPDVIKWERRVIPGCTRSIYSATGKWTKEYTLQTRKDVEKWWHQRIKEQASKIS
EADKSKPKFYVLSMFPYPGKLLHMGHVRVYTISDTIARFQKMRGMQVINPMGWDAFGLPAENAAVERNLHPQSWT
QSNIKHMRKQLDRLGLCFSDREITTCLPDYYKWTQYLF IKLYEAGLAYQKEALVNWD PVDQTVLANEQVDEHGC
SWRSGAKVEQKYLRQWF IKTTAYAKAMQDALADLPEWYGIKGMQAHWIGDCVGCCHLDFTLKVHGQATGEKLTAYT
ATPEAIYGTSHVAISP SHRLLHGHSSLKEALRMALVPGKDCLTPVMAVNMLTQQEVV VILAKADLEGLSLDSKIG
IPSTSS EDTILAQTLGLAYSEVIETLPDGTERLSSSAEFTGMTRQDAFLALTQKARGKRVGGDVTS DKLKDWLIS
RQRYWGTP IPIVHCPVCGPTFPVPLEDLPVTLPNIASFTGKGGPPLAMASEWVNCSCPRCKGA AKRETD TMDTFVD
SAWYYFRYTDPHNPHSPFNTAVADYWMPVDLY IGGKEHAVMHLFYARFFSHFCHDQKMVKHREPFHKLLAQGLIK
GQTFRLPSGQYLQREEVDLTGSVPVHAKTKEKLEVTWEKMSKSKHNGVDPEEVVEQY GIDTIRLYILFAAPPEKD
ILWDVKTDALPGVLRWQQLWTLTTRFIEARASGKSPQPQLLSNKEKAEARKLWEYKNSVISQVTTHFTEDFSLN
SAISQLMGLSNALSQASQSVILHSPEFEDALCALMVMAAPLAPHVTSEIWAGLALVPRKLC AHYTW DASVLLQAW
PAVDPEFLQQPEVVQMAVLINNKACGKIPVPQQVARDQDKVHEFVLQSELGVRL LQGRS IKKSFLSPRTALINFL
VQD

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FIGURE 19

TATATTGGCAGTTATTGAGGGTAAAGCAATATATTGTAACAGAATGTATAAAATATTTTTGATAAAACAGTCTATA
TTTTATTAAAAAATGAATTATAACCCATTTTCAGTTTTGCCTGTCATCATAAGAGTGAGCACTCCATTGCTTTCTT
TCCTGGCCACACTGCTACAATCCAGCACTAACTATCCATGTCCAGGGTAAGGATCGAGATCGAGAAGCCCACACT
GCCAGTGAAAAAGCTACGTCTTTACTGCATAAAATTAGAGGAAGCAATTTTCGGAACAACGGAACCTTCAAACCTATA
AATACTGAATTATCGAACACTTGCCAGGCACTTCAGCAGAAGACAAGGAACTGAAGAAGCTTTTTAGATGAGGA
ATTTCTCACTATGATTCCCTGTCCTGCGCAGATGCAATTCAACAACCTCTTCAAGAAAAATTGAAGCAGTGTG
CCACAACTATATGGTGGTCAAGAAGCAAGAATACATCAGACACCCCTGACCTTGAAACATACGTGCTGGTACAC
ACCTCTGCTGGATGCTCTTATCTCTGGATAGTTTTACAGCAGTTCCAACCCCTGGAATCAACACCTTTCTCAGGTGT
AGCCAACCAAATCCACACTCTGTGTGAAAGGCCACATATGGAGAAGTAAAGGATGGTGTCTTGGATGTAAAAAG
ACAACACAAGTGCCAGGCCCCACAAGTGGCCCCAGCCCAGGAACGAATCTCTCAGGCTGCATCAGGATGAATGA
TGACCCAAGTATGGAAGAGAATGGTGTGTAACGCGTGTGTCTGAGAGCCTGCTGCAGTCCAGGGGATATTCCTC
ACTACCATTACCCAGACACACTTCATCGACAGACGGTACTATAACTTCAAGTGATCCTGGATTAGAAATTCTGAA
TATGGCTTCTTGTGACCTTGACAGAACTCGCTCTGTAAGAAAGAGGAGGATACAAGATCAGCTTCTCCCACGAT
AGAGGCCCAAGGCACAAGTCCAGCTCATGATAATATTGCATTCCAAGACTCTACGAGTAAGGATAAAACCATATT
AAATCTGGAAGCCAAAGAGGAACCAGAAACAATAGAAGAACATAAAAAAGAACATGCTTCAGGAGACTCTGTGGT
TTCCCTCTTCTGTAACTGTGAAATCGGTTAACGTTAGACAAAGTGAGAACACTTCTGCTAATGAGAAGGA
GGTGGAGGCAGAATTTCTCAGATTATCTTTGGGATTTAAGTGTGACTGGTTTACCTTGGAGAAGAGAGTGAAGCT
TGAAGAGAGGTCCCGTGACTGGGCAGAAGAAAATTTGAAGAAAGAAATCACTAACTCTTTAAACTATTAGAGTC
TTTAACACCTCTGTGTGAAGATGACAACCAGGCACAGGAAATCATTAAGAAGCTGGAGAAGAGTATAAAGTTTCT
TAGCCAGTGTGCAGCACGAGTGGCCAGTAGGGCTGAGATGTTGGGAGCCATCAATCAGGAAAGCCGGGTTAGTAA
AGCAGTTGAAGTGATGATTTCAGCACGTAGAAAACCTTGAAGAGGATGTATGCCAAAGAGCACGCTGAATTAGAAGA
ACTGAAACAGGTTCTTCTGCAGAATGAAAGGTCTTTCAATCCTCTTGAAGATGATGATGACTGCCAAATTAAGGA
ACGTTTCAGCTTCTCTAAACTCCAAGCCATCTTCTCTACGAAGAGTGACTATTGCCTCTTTACCCAGAAATATTGG
AAATGCAGGAATGGTGGCTGGGATGGAATAATGATCGATTTCAGTAGAAGGTCAAGCAGTTGGCGTATTTTGGG
GTCAAAGCAGAGTGAACACCGTCCCTCATTACCTCGATTATTATAGCACCTATTCTGGGCAGATGCTGAAGAAGA
AAAATGTGAACATAAACTAAAGATGACTCAGAGCCATCTGGAGAAGAAACAGTAGAAAGGACAAGGAAGCCAAG
TCTTTCTGAAAAGAAAAATAATCCATCAAAGTGGGATGTCTCTTCAGTTTATGACACAATAGCTTCTGGGCAAC
AAATCTCAAGTCCTCCATCAGAAAGGCTAATAAGGCCCTCTGGCTCTCTATTGCATTTCATTGTACTGTTTGCAGC
TTTGATGAGCTTCTCAGAGGCCAATTATTCCAGAAGTCTGTGGATGCCGCTCCACACAGCAAGAGGACTCATG
GACGTCTCTAGAACATATCTTGTGGCCATTTACCAGACTCCGACACAATGGGCCACCACCAGTGTGACAGCAGGA
CATCCTAATATATGGATCTTGATTTTTAAGTTTCAGTATCTGAACTTCGTAAATTAGTAACTTTTAGCTGGGAAA
GTATAGCATGAAACCAGAGGTTCTCAGAATGACCGTAAGATAGCTTACATTTCTCTTTTGCCTTTATCTCCCC
AACTAAAATACAATGGG

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FIGURE 20

MESTPFSGVANQIHTLCERPTYGEVKDGDALDVKRQHKCPGPTSGPSPGTNLSGCIRMNDPSMEENGVERVCPE
LLQSRGYSSLPLPRHTSSTDGTITSSDPGLEILNMASCDLDRNSLCKKEEDTRSASPTIEAQGTSPAHDNIAFQD
STSKDKTILNLEAKEEPETIEEHKKEHASGDSVVSPLPVTTVKSVNVRQSENTSANEKEVEAEFLRLSLGFKCDW
FTLEKRVKLEERSRDWAEENLKKEITNSLKLLESLTPLCEDDNQAQEI IKKLEKSIKFLSQCAARVASRAEMLGA
INQESRVSKAVEVMIQHVENLKRMYPKEHAELEELKQVLLQNERSFNPLEDDDDCQIKKRSASLNSKPSSLRRVT
IASLPRNIGNAGMVAGMENNDRFSRRSSSWRILGSKQSEHRPSLPRFISTYSWADAEKCEKTKDDSEPSGEE
TVERTRKPSLSEKKNNPSKWDVSSVYDTIASWATNLKSSIRKANKALWLSIAFIVLFAALMSFLTGQLFQKSVD
APTQQEDSWTSLEHILWPFTRLRHNGPPP

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FIGURE 21

ATGGTGCTGTGCCCCGGTGATTGGGAAGCTGCTGCACAAGCGCGTGGTGCTGGCCAGCGCCTCCCCACGCCGTCAG
GAGATCCTCAGCAACGCGGGTCTCAGGTTTGAGGTGGTCCCCTCCAAGTTTAAAGAGAAGCTGGACAAAGCCTCC
TTCGCTACTCCGTATGGGTACGCCATGGAGACCGCCAAGCAGAAGGCCCTGGAGGTGGCCAACCGGCTATACCAG
AAAGACCTGCGGGCCCCCGACGTGGTCAATTGGAGCGGACACGATCGTGACGGTCGGGGGGGCTGATTCTGGAGAAG
CCGGTGGACAAGCAGGACGCCTACAGGATGCTGTCCCGGTTGAGTGGGAGAGAAACACAGCGTGTTACAGGTGTC
GCGATCGTCCACTGCTCCAGCAAAGACCATCAGCTGGACACCAGGGTCTCGGAATTCTACGAGGAAACGAAGGTG
AAGTTCTCGGAGCTGTCCGAGGAGCTGCTCTGGGAATACGTCCACAGCGGGGAGCCCATGGACAAAGCTGGCGGC
TACGGTATCCAGGCCCTGGGCGGCATGCTGGTGGAGTCCGTACACGGGGACTTTCTGAACGTGGTGGGATTCCCCG
CTGAACCACTTCTGCAAGCAGCTGGTGAAGCTCTACTACCCGCCCCGTCCGGAGGACCTGCGGCGGAGTGTCAAG
CACGACTCCATCCCGGCCGCGGACACCTTCGAAGACCTCAGTGACGTGGAGGGGGGCGGCTCGGAGCCCACTCAG
AGGGACGCGGGCAGCCGCGATGAGAAGGCCGAGGCGGGAGAGGCGGGACAGGCCACGGCAGAGGCTGAGTGTAC
AGGACTCGGGAGACCCTGCCTCCGTTCCCGACACGCCTCCTGGAGCTGATTGAGGGCTTTATGCTATCCAAGGGC
CTGCTACCCGCTTGCAAAGTGAAGGTGTTGATTTATTAAAAGATGAAGCACCCCAGAAAGGCTGCGGATATTGCC
AGCAAAGTGGACGCCTCTGCGTGTGGAATGGAGAGGCTTCTGGACATCTGTGCTGCCATGGGGCTCCTGGAGAAG
ACAGAGCAAGGTTACAGTAACACAGAGACAGCGAACGTCTACCTGGCATCGGATGGCGAATACTCTCTGCACGGC
TTCATCATGCACAATAATGACCTCACATGGAACCTCTTTACATACCTGGAGTTTGCCATCCGAGAGGGAACAAAC
CAGCACCAAGGGCGTTGGGGAAGAAGGCGGAAGATCTGTTCCAGGATGCGTACTACCAGAGCCCGGAGACGCGG
CTGAGGTTTCATGCGGGCCATGCACGGCATGACGAAGCTGACTGCGTGCCAGGTGGCCACGGCCTTCAATCTGTCC
CGCTTCTCCTCCGCCTGCGACGTGGGAGGCTGCACGGGTGCACTGGCCCCGAGAGCTGGCCCCGTGAGTACCCTCGT
ATGCAGGTGACTGTGTTTGACCTCCAGACATTATCGAGCTGGCCGCCCACTTCCAACCCCCCGACCGCAGGCA
GTGCAGATCCACTTCGCAGCAGGTGACTTTTTTCAGGGACCCCCCTCCCCAGCGCTGAGCTGTACGTCCTGTGCCGG
ATCCTGCATGACTGGCCAGACGACAAAGTCCACAAGTTACTCAGCAAGGTCGCCGAGAGCTGCAAGCCAGGGGCC
GGCCTGCTGCTGGTGGAGACGCTCCTGGATGAGGAGAAGAGGGTGGCGCAGCGCGCCCTGATGCAGTCACTGAAC
ATGCTGGTGCAGACTGAAGGCAAGGAGCGGAGCCTGGGCGAGTATCAGTGCTTGCTGGAGCTGCACGGCTTCCAC
CAGGTGCAGGTGGTGCATTGGGGGGTGTCTGGATGCCATCTTGCCACCAAAGTGGCCCCCTGAAGCCCAGGCA
GCATGTTCAATTATAG

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FIGURE 22

MVLCFVIGKLLHKRVVLASASPRRQEILSNAGLRFVVP SKFKEKLDKASFATPYGYAMETAKQKALEVANRLYQ
KDLRAPDVVIGADTIVTVGGLILEKPVDKQDAYRMLSR LSGREHSVFTGVAIVHCSSKDHQLDTRVSEFYEEKV
KFSELSEELLWEYVHSGEPMKAGGYGIQALGGMLVESVHGDFLNVVGFP LNHFCKQLVKLYPPRPEDLRRSVK
HDSIPAADTFEDLSDVEGGGSEPTQRDAGSRDEKAEAGEAGQATAEAECHRTRETLPFPTRLLELIEGFMLS KG
LLTACKLKVFDLLKDEAPQKAADIASKVDASACGMERLLDICAAMG LLEKTEQGYSNTETANVYLASDGEYSLHG
FIMHNNDLTWNLFITYLEFAIREGTNQHHRALGKKAEDLFQDAYYQSPETRLRFMRAMHG MTKLTACQVATAFNLS
RFSSACDVGGCTGALARELAREYPRMQVTVFDLPDI IELAAHFQPPGPQAVQIHFAAGDFFRDPLPSAELYVLCR
ILHDWPDDKVHKL LSKVAESCKPGAGLLL VETLLDEEK RVAQRALMQSLNMLVQTEGKERSLGEYQC LLELHGFH
QVQVVHLGGVLDAILPPKWPPEAQAACSL

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FIGURE 23

CGCCTCTCCCAAAGTCTAGCCGGGCAGGGGAACGCGGTGCATTCTGACCGGCACCTGGCGAGGCTCATGCGTCC
CGTGAGGGCGGTTTCTCGAGCCTGGGGGCGCTCAGATTGCTTTGGAGACGCTGAGAGAACCTTTGCGAGAGCGCC
GGTTGACGTGCGGAGTGCGGGGCTCCGGGGGACTGAGCAGCACGAGACCCCATCTCCCTCCGGGTTTTTCACAC
TGGGCGAAGGGAGGACTCCTGAGCTCTGCCTCTTCCAGTAACATTGAGGATTACTGTGTTTTGTGAGAGCTCGCT
AGGCGCCCTAAGCAACAGAGTTCTGAGAAATCGAGAAACATGATAAGGAATTGGCTGACTATTTTTATCCTTTTT
CCCCTGAAGCTCGTAGAGAAATGTGAGTCAAGCGTCAGCCTCACTGTTTCTCTCTGTCGTAAAGCTGGAGAACGGC
AGCTCGACCAACGTGAGCCTCACCTGCGGCCACCATTAAATGCAACCCTGGTGATCACTTTTGAAATCACATTT
CGTTCCAAAATATTACTATCCTTGAGCTCCCCGATGAAGTTGTGGTGCCTCCTGGAGTGACAAACTCCTTTTT
CAAGTGACATCTCAAAATGTTGGACAACCTACTGTTTATCTACATGGAAATCACTCCAATCAGACCGGCCCGAGG
ATACGCTTTCTTGTGATCCGCAGCAGCGCCATTAGCATCATAAACCAGGTGATTGGCTGGATCTACTTTGTGGCC
TGGTCCATCTCCTTCTACCTCAGGTGATCATGAATTGGAGGCGGAAAAGTGTCATTGGTCTGAGCTTCGACTTC
GTGGCTCTGAACCTGACAGGCTTCGTGGCTACAGTGTATTCAACATCGGCCTCCTCTGGGTGCCCTACATCAAG
GAGCAGTTTCTCCTCAAATACCCCAACGGAGTGAACCCCGTGAACAGCAACGACGTCTTCTTCAGCCTGCACGCG
GTTGTCTCACGCTGATCATCATCGTGAGTGTGCCTGTATGAGCGCGGTGGCCAGCGCGTGTCTGGCCTGCC
ATCGGCTTCTGGTGCTCGCGTGGCTCTTCGCAATTTGTACCATGATCGTGGCTGCAGTGGGAGTGATCACGTGG
CTGCAGTTTCTCTTCTGCTTCTCCTACATCAAGCTCGCAGTCACGCTGGTCAAGTATTTTCCACAGGCCTACATG
AACTTTTACTACAAAAGCACTGAGGGCTGGAGCATTGGCAACGTGCTCCTGGACTTCACCGGGGGCAGCTTCAGC
CTCCTGCAGATGTTCTCCTCAGTCTTACAACAACGACCAAGTGGACGCTGATCTTCGGAGACCCAACCAAGTTTGGA
CTCGGGGTCTTCTCCATCGTCTTCGACGTGCTCTTCTTATCCAGCACTTCTGTTTGTACAGAAAGAGACCGGGG
TATGACCAGCTGAACTAGCACCCAGGGACCCAGTGTACCCAGCCTCTGGCCTCGTGCCCTGCTGGGGAAGGCCTC
ACCCAGCGAAGGCCGAGAAAGCGTTGGGCCCTGGCACACAGGGCTGGCTCAGTGTGCGGACAGAGGAGACCACT
CTGCTCCTGGGGCCAGAGGCCATTCAATAGCCTGCCTTTCGTCCGGGCCCCCTCCTGGGCCTCCCCGGCCAGGCACG
TGGCACCGTCGCCTTGACACCGCCATCTCTTTTCTTTAAGGCTTCAGGCAGCGCGCACAGGCTCTGGCAGCCGTC
TCAGGCAGGACTGGGCACCAAGCTTGACGCCGAAGGCCTTGCCCCAAACTACCAGCGTTTCTGCAAGCAGCTTGA
AGGGCTGACCTTGACGCCGGGTGAGCCAAGGGCACTTTGCTGCCACCGCTGCATTCCCAGAGATCAAGCAGCCCG
GTGCCGTGGCCAGTGAACCTCAGAGGTGCTGGTGGACGGGCTAGGACTTTGGGGTTAGGCCATGGGGCTCTTTCTC
TGAAGGCCACTTTCTGACGTACTCTCTGTACATAACTCAGCGTCCGTGACTGCAGTAACAGCCAGCCCTACCCA
GAGTATTTCTGAGCCATGAGGGGCCCCACCAGATTGGTTCTGAATTGGATTGATGCCCAGCGCATTAGCATAGTAA
CTCCTTTTCTGAGATTTTTTGGAGGGACGTTTGGAAAGTGGCTTACTCTCTTCTGCCCTCTCTCCTACCTCCACCTTCT
CAGATGAGCCCCATCTGAGCACATCCAGCTGCTCCTTACCCAGCATCTGGAGTACAGGACATAGCTCTCTCCTGC
TACCAGTCTGTGCCCTTAGAGGTCGTTAGGCCTGCCAAACGGCGACCAGCTCCCCTGGAGCGAGGGCAGGCCCTT
CCCTCTCTTTCCCCAGACACCTACTTGAGACTACCAATTTCTGGCCTGTTGAGGAGCCTCAGATAAGTATTTGT
ACTTGAGACCACCTCACACAATCTGTATGGGCCCAACCCTGATCTCAAACCTCCTTCCCTCTGCCCAAAGCTGTC
CTTCTATGGCAGGAGGGGTGGGGTCCCAGGACGTGCCTCATACATGACTTGAGCTTGTGAGTCCACTGAGTTT
CCTTCTACGAGATCAACGCGAGGGGCTGTATCTTGAATTAAAGCCTACTCGCTTCCTTTC

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FIGURE 24

MIRNWLTIIFILFPLKLVEKCESSVSLTVPPVVKLENGSSTNVSLTLRPPLNATLVITFEITFRSKNITILELPDE
VVVPPGVTNSSFQVTSQNVGQLTVYLHGNHSNQTGPRIRFLVIRSSAISIINQVIGWIYFVAWSISFYPPQVIMNW
RRKSVIGLSFDFVALNLTGFVAYSVFNI GLLWVPYIKEQFLLKYPNGVNPVNSNDVFFSLHAVVLTLLIIVQCCL
YERGGQRVSWPAIGFLVLAWLFAFVTMIVAAGVITWLQFLFCFSYIKLAVTLVKYFPQAYMNFYYKSTEGWSIG
NVLLDFTGGSFSLQMFLQSYNNDQWTLIFGDPTKFGGLGVFSIVFDVVFFIQHFCLYRKRPGYDQLN

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FIGURE 25

CTTACAACCTCCGCGCGGCCTCGGCCCTCGCGCCGCCCGCCCCACAACAAACTCAGCGCAGCGCTCCCGGGCGC
CCGGTTCAGAGCGACCTGCGGCTCAGAGCGGAGGGGAGACTGACCGGAGCGCGGATCGGGACAGCGGCCGGGACA
GCGGCGAGACGCGCGTGTGTGAGCGCGCCGGACCAAGCGGGCCAGAAGCGGGTCTGCAGCCCAGAGGGCACCTT
CTGCAAACATGTCTGTGGATCCCTATCCAGCAAAGCTCTAAAGATCAAGCGAGAGCTGAGCGAGAACACGCCCGC
ACCTGTTCGGACGAGGCGCTGATGGGGCTGTCTGGTGC GCGAGCTGAACCGGCATCTGCGCGGGCTCTCCGCCGAGG
AGGTGACACGGCTCAAGCAGCGGCGCCGCACACTCAAAAACCGTGGCTACGCCGCCAGCTGCCGCGTGAAGCGCG
TGTGCCAGAAGGAGGAGCTGCAGAAGCAGAAGTCGGAGCTGGAGCGCGAGGTGGACAAGCTGGCGCGCGAGAACG
CCGCCATGCGCTTGGAGCTCGACGCGCTGCGCGGCAAGTGCAGAGCGCTGCAGGGCTTCGCGCGCTCCGTGGCCG
CCGCCCCGCGGGCCCCGCCACGCTCGTGGCGCCGGCCAGCGTCATACCATCGTCAAGTCCACCCCGGGCTCGGGGT
CTGGCCCCGCCACGGCCCCGACCCCGCCACGGCCCCGGCTCCTGTCTCCTAGTGCCCCGCCCCCGCCATGCCTCA
GCCACGCCCCCTCCGGCCTCAGCTCCCTCCCCAAAGTGCCTGAGCGCCGCTCTGTGCCAGGTCCCATTCTCTG
CAGCACTGGCCCCCTTGGTGCACACACATTCCCTTCGTGGGCCCTGTCTTCTCTTGACGCCCCCAAAGTGGGAC
CGAATGACCCTGGGAAGGGGAAGTTGGGTAGGTTGGGGATGGGGCAGAGGTCTGGATCTGGGATCGCCCTTGGCT
GAAAGTTTAGCCTTTTTAGATTGAGAGATACAGAGCCGGCTTAGAGAACAGCTGTTGGGGGAGAAGAGGGGACCC
CTCATCTTGGAACTGCTCTTATTGTGCCAATATGCCCTCCAAACCTCCCAGGATTCAAAGCTAGGTTTGGCTG
TCTGTGACTTACGGGACCGTCTCTGCTGAGAAATTGCACTGAAGAGATGCCCCACCTCTGGTTGGGCCTGGGGGT
GCCTGGCCTTCCGAACTAAAAGAGTGGGTGGGAAGACTAGTGAAACCCAGTTCACGGATGGGGAAACAGGCCTG
AGGTCACATTTCACTTAGTGGTTGTGTTGGGACCAAACCTGGGTGTCTCACTGCTGAGTCCAGCCATGGTTTT
CAGGGGGACAGTGAGACAGGGACTCAGAAATGTGGTGGGAGGGCCTCCCTGGCTGGGAGACCGCTCTCTGCAAGG
GAGGGGGAGAGAAGCAGAGGGGAGAGAGAAGGTGACACGGATGGAAGAGTGGGAAGGAGCTGGCCTGGCTCAGCCC
TAGGCTGTCCCTGCAGCCAGGGTGTCCGGGGGCTGGCCAGTCAGAGAAAGGGGGCCATGGACTGCTGTGGCAAAT
AGGGAGACAAGGAGACAGACCCCTGCAGTCCTACTACAGTCTGGAGTGGGGTCTTAAGAAGAAGGGTCCACCTCA
ACCCCTGTCACTGTCCACTGTGGGTGGGGGCTGACCCCTGCCTTTGATTGTCATTCTCTGGGAAGCCCAGTCT
CAGTCCCTCCCCAACACTGTCCACACTGCCCTCCCCACTGTTTATTTATTGCACGGATCTAAGTTATTCTCCC
CAGCCAGAGCCCCGAGCTCCTGCTCCCTGGGAAAAGTGGCGTATGGCCCTGAGCTGGGCTTTATATTATATATCTG
CAAATAAATCACATTTTATCTTATATTTAGGGAAAGCCGGAGAGCAACAACAAAAAATGTTTAAGCCGGGCGCGG
TGGCTCACATCTGTAATCCAGCACTTTGGGAGTCCAAGGAGGGGGATCGCTTGAGTCCAGGAGTTTGAGACCAG
CCTGGACAACATGGTGAAACCCCGTCTCTACAAAAAATACAAAAATTAGCCATGCATGGTGGCTCATGCCTGTAG
TCCCAGCTACTTGGGAGGCTGAGGCAGGAGGATCACTTAAGCCCAGAAGGCAGAGGTTGTAGTGAGCTGAGATCG
CACCCTGCACTCCAGCCTGGGCAACATAGCAAAATCCTGTCTCAAAAAAAGTTAAAAAATATTGCCCGGCTC
CTAGAATTTATTTATTTTCTGACTTACAGCAAGCGAGTTATCGTCTTCTGTATTTTGTAGACTTTCTAAATAAAG
TCAAATTTCTTTTCTTTTCCACAGAAAAA

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FIGURE 26

MSVDPLSSKALKIKRESENTPHLSDEALMGLSVRELNRHLRGLSAEEVTRLKQRRRTLKNRGYAASCRVKRVCO
KEELQKQKSELEREVDKLARENAAMRLELDALRGKCEALQGFARSVAAARGPATLVAPASVITIVKSTPGSGSGP
AHGPDPAHGPFASCS

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FIGURE 27

GCGGAGCGCGCTCCCAGCGAAAAGCAGCAGGGCAGGGATCTGCGTTGGAGGAAGGGACTGCTCTGGTGCTAGAA
TGCTGTGCGTCGGAAGGCTGGGCGGCTTGGGAGCCAGAGCAGCAGCTCTGCCGCCCCGCCGGGCGGGCCGGGGAA
GCCTCGAAGCCGGGATCCGGGCCCCGAAGGGTCAGCACCAGCTGGTCTCCCGTGGGCGCCGCTTCAATGTCAAGC
CCCAGGGCAGCCGCTTGGACCTGTTGCGCGAGCGGGCGCGTCTTTTTGGAGTTCCTGAGCTGAGTGCCCCAGAAG
GATTTTCATATTGCACAAGAAAAAGCCTTGAGAAAGACAGAATTGCTTGTGGACCGTGCATGTTCCACCCACCTG
GGCCCCAGACCGTGCTGATCTTCGATGAGCTCTCGGATTCTTATGCAGAGTGGCCGACTTGGCTGATTTTGTGA
AAATCGCTCACCTGAGCCAGCATTCAGAGAAGCTGCGGAAGAAGCTTGTAGAAGTATTGGCACCATTGGTAGAGA
AGTTGAACACAAATGTGGATTTATATCAAAGTTTGCAAAATTACTAGCTGATAAAAACTTGTGGATTCCCTTG
ATCCAGAAACAAGGCGAGTGGCTGAACTGTTTATGTTTGATTTTGAAATTAGTGGAATCCATCTAGACAAACAA
AGCGTAAAAGAGCAGTGGACCTCAATGTTAAATCTTGGATTTGAGTAGTACATTTCTTATGGGAACCAATTTTC
CCAACAAGATTGAGAAGCATCTCTTACCAGAACACATTTCGTCGTAACCTTACATCTGCTGGGGATCATATCATAA
TTGATGGTCTCCACGCAGAATCACCAGATGACTTGGTGCGAGAAGCTGCTTATAAAATTTTCTTTATCCCAATG
CTGGTCAATTGAAATGTTTAGAAGAATTGCTCAGCAGCAGAGATCTTCTGGCAAAGTTGGTGGGGTATTCCACGT
TTTCTCACAGGGCTCTCCAAGGAACGATAGCTAAAAATCCAGAGACTGTCATGCAGTTCCTTGAAAACTATCTG
ACAACTTTCTGAAAGAACTCTGAAAGATTTTGAGATGATACGAGGGATGAAAATGAACTGAATGCTCAAAATT
CCGAAGTAATGCCCTGGGACCCCCCTTACTACAGTGGTGTGATTTCGTGCAGAAAGGTATAATATTGAGCCAGCC
TATATTGCCGTTTTTCTCTCTTGGAGCATGCATGGAAGGCCTGAATATTTTGCTTAACAGACTGTTGGGGATTT
CATTATATGCAGAGCAGCCTGCAAAAGGAGAGGTGTGGAGCGAAGATGTCCGAAAACCTGGCTGTTGTTTCATGAAT
CTGAAGGATTGTTGGGGTACATTTACIGTGATTTTTTTTTCAGCGAGCAGACAAACCACATCAGGATTGCCATTTCA
CTATCCGTGGAGGCAGACTAAAGGAAGATGGAGACTATCAACTCCCCTTGTAGTTCTTATGCTGAATCTTCCCC
GTTTCTCAAGGAGTTCTCCAACCTTGCTAACTCCTGGCATGATGGAAAACTTTTTCCATGAAATGGGACATGCCA
TGCAATTCATGCTAGGACGTACTCGTTACCAACACGTCACTGGGACCAGGTGCCCTACTGATTTTGCTGAGGTTT
CTTCTATTCTGATGGAGTACTTTGCAAATGATTATCGAGTAGTTAACCAATTTGCCAGACATTATCAGACTGGAC
AGCCACTGCCAAAAAATATGGTGTCTCGTCTTTGTGAATCTAAAAAGGTTTGTGCTGCAGCTGATATGCAACTTC
AGGTCTTTTATGCCACTCTGGATCAAATCTACCATGGGAAGCATCCCCTGAGGAATTCAACCACAGACATTCTCA
AGGAAACACAAGAGAAATTTCTATGGCCTACCATATGTTCCAAATACTGCCTGGCAGCTGCGATTTCAGCCACCTCG
TGGGGTATGGTGCTAGATATTACTCTTACCTCATGTCCAGAGCGGTGCGCTCCATGGTTTGAAGGAGTGTTTTT
TACAGGATCCTTTCAACAGGGCTGCCGGGGAGCGCTATCGCAGGGAGATGCTGGCCACGGTGGAGGCAGGGAGC
CCATGCTCATGGTTGAAGGTATGCTTCAGAAGTGTCCTTCTGTTGATGACTTCGTAAGTGCCCTCGTTTCCGACT
TGGATCTGGACTTCGAACTTTCTCATGGATTCTGAATTAAAAGAAACACTCTACACCTCTAATCAAGGTCATGT
AGTAATGACTTTGTTATAAATGCTACAGCTGTGAGAGCTTGTCTGATTGTTTCATTGTTTCGCTTCTGTAAATTC
TGAAAACTTTAAACTGGTAGAACTTGAATAAATAATTTGTTTTAATTAAAAA

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FIGURE 28

MLCVGRLGGLGARAAALPFRRAGRGSL EAGIRARRVSTSWSPVGAAFNVKPQGSRLDLFGERARLFGVPELSAPE
GFHIAQEKALRKTELLVDRACSTPPGPQTVLIFDELSDSLCRVADLADFVKIAHPEPAFREAAEEACRSIGTMVE
KLNTNVDLYQSLQKLLADKKLVDSLDPETRRVAELFMDFEISGIHLDKQKRKRAVDLNVKILDLSSTFLMGTNF
PNKIEKHLLPEHIRRNFTSAGDHIIIDGLHAESPDDL VREAAYKIFLYPNAGQLKCLEELLSSRDLLAKLVGYST
FSHRALQGTIAKNPETVMQFLEKLSDKLSERTLKDFEMIRGMKMKLNAQNSEVMPWDPPYYSGVIRAERYNIEPS
LYCPFFSLGACMEGLNILLNRLLGISLYAEQPAKGEVWSE DVRKLA VVHESEGLLGYYICDFFQRADKPHQDCHF
TIRGGRLKEDGDYQLPLVVLMLNLPRSSRSSPTLLTPGMMENLFHEMGHAMHSMLGRTRYQHVTGTRCPTDFAEV
PSILMEYFANDYRVVNQFARHYQTGQPLPKNMVSR LCE SKKVCAAADMQLQV FYATLDQIYHGKHPLRNSTTDIL
KETQEKFYGLPYVPNTAWQLRF SHLVGYGARYYSYLMSRAVASMVWKECFLQDPFNRAAGERYRREMLAHGGGRE
PMLMVEGMLQKCPSVDDFVSALVSDLDLDFETFLMDSE

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FIGURE 29

TTTGCAAATAGTAACGACAAAGATGATCAAGTTTTAAATTGCCATTTGGCAGTGAAGGTGCTATCCCCGGAAGAT
GGAAAAGCAGATATTGTGAGAGCCGCTCAGGACTTTTGCCAGTTAGTAGCCCAGAAGCAAAGGAGACCCAAAGAT
TTGGATGTAGATATGTTAGTTTACTCAGTTCAAATGGTTGTCCTGATCCTGATTTAGTACTGAAGTTCGGTCCCTG
TGGACAGCACACGAGGCTTTTCTTACCTGGCACATCAGATTGACTGAGACTGTCTCTTTGCCTTCCCATCTAAACA
TCAGTTATGAGGACTTTTTCTCTGCCCTTCGTCATTATGCAGCCTGTGAACAGCGTCTGGGAAAGTCGTGGTTCAT
TGGTTGCATAATTCCATTTGAGCTTATGGAGGAAAGGACCAAGTGACTCTGATTTTAGAAAGCACCTATGAAACC
CTGTACACACCTATGAAACCCTGTACACACCTAGTTCATAATCTTCATAATTTATCAACAAACACAAAAAAGTGT
CTTACTTGAGAGTGAGTGTGTGCGTGTGTGCGTGCACACATGTGCACGTTTGTATGTGTGGAAATAAACATAAAT
GGGGACGTGTTGGAGAAGGAAATACATAGACCTACAACCTTTGAGCATATAGCAGTGATGTTTTAGGAACTGAAAT
GTCACACTTAATAAAGTCTTCAGCCCAGCTACTTCCCTGTTTTCGTGGGGAGAAGAGGGCCTGATTAGAACTGTT
CTGGTTGTGTTTGGCGGGAGGGGAATAAATTTTGTTTCAGTCCTTCTTAGTGACCAAACTTTAATTTTAAAGAATA
ATATATTGACTTACTGAACTGAAGCATTCTGAGTTGAAAGGAGCTCCAGAGGAAAGGAGTTCTGTGTTGCTCACA
TGTTAAAGCTTGCTCACCTTCAGAGCAGAGGAATACCTATCTACAGATATCCGCCCATTTTCATCTCTCTTCATT
ATAGTCAAACAGTGTGACTTGAGAGTGTTG

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FIGURE 30

FANSNDKDDQVLNCHLAVKVLSPEDGKADIVRAAQDFCQLVAQKQRRPKDLDVDMLVYSVQMVLILI

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FIGURE 31

GAATTCTGCGGAGCCTGCGGGACGGCGGGGGTTGGCCCGTAGGCAGCCGGGACAGTGTGTACAGTGTGTTTGGG
CATGCACGTGATACTCACACAGTGGCTTCTGCTCACCAACAGATGAAGACAGATGCACCAACGAGGGTCTGGAAT
GGTCTGGAGTGGTCTGGAAGCAGGGTCAGATACCCCTGGAAAACTGAAGCCCGTGGAGCAATGATCTCTACAGG
ACTGCTTCAAGGCTGATGGGAACCACCTGTAGAGGTCCATCTGCGTTCAGACCCAGACGATGCCAGAGCTATGA
CTGGGCCTGCAGGTGTGGCGCCGAGGGGAGATCAGCCATGGAGCAGCCACAGGAGGAAGCCCCTGAGGTCCGGGA
AGAGGAGGAGAAAGAGGAAGTGGCAGAGGCAGAAGGAGCCCCAGAGCTCAATGGGGGACCACAGCATGCACTTCC
TTCCAGCAGCTACACAGACCTCTCCCGGAGCTCCTCGCCACCCCTCACTGCTGGACCAACTGCAGATGGGCTGTGA
CGGGGCCTCATGCGGCAGCCTCAACATGGAGTGCCGGGTGTGCGGGGACAAGGCATCGGGCTTCCACTACGGTGT
TCATGCATGTGAGGGGTGCAAGGGCTTCTTCCGTGCTACGATCCGCATGAAGCTGGAGTACGAGAAGTGTGAGCG
CAGCTGCAAGATTGAGAAGAAGAACGCAACAAGTGCCAGTACTGCCGCTTCCAGAAGTGCCTGGCACTGGGCAT
GTCACACAACGCTATCCGTTTTGGTTCGGATGCCGGAGGCTGAGAAGAGGAAGCTGGTGGCAGGGCTGACTGCAAA
CGAGGGGAGCCAGTACAACCCACAGGTGGCCGACCTGAAGGCCCTTCTCCAAGCACATCTACAATGCCTACCTGAA
AAACTTCAACATGACCAAAAAGAAGGCCCGCAGCATCCTCACCGGCAAAGCCAGCCACACGGCGCCCTTTGTGAT
CCACGACATCGAGACATTGTGGCAGGCAGAGAAGGGGCTGGTGTGGAAGCAGTTGGTGAATGGCCTGCCTCCCTA
CAAGGAGATCAGCGTGCACGTCTTCTACCGCTGCCAGTGACCACAGTGGAGACCGTGCGGGAGCTCACTGAGTT
CGCCAAGAGCATCCCCAGCTTCAGCAGCCTCTTCTCAACGACCAGGTTACCTTCTCAAGTATGGCGTGCACGA
GGCCATCTTTCGCCATGCTGGCCTCTATCGTCAACAAGGACGGGCTGCTGGTAGCCAACGGCAGTGGCTTTGTAC
CCGTGAGTTTCTGCGCAGCCTCCGCAAAACCTTCAGTGATATCATTGAGCCTAAGTTTGAATTTGCTGTCAAGTT
CAACGCCCTGGAACCTTGATGACAGTGACCTGGCCCTATTTCATTGCGGCCATCATTCTGTGTGGAGACCGGCCAGG
CCTCATGAACGTTCCACGGGTGGAGGCTATCCAGGACACCATCCTGCGTGCCCTCGAATTCCACCTGCAGGCCAA
CCACCTTGATGCCAGTACCTCTTCCCCAAGCTGCTGCAGAAGATGGGTGACCTGCGGCAACTGGTCCACCGAGCA
CGCCAGATGATGCAGCGGATCAAGAAGACCGAAACCGAGACCTCGCTGCACCCTCTGCTCCAGGAGATCTACAA
GGACATGTACTAACGCGGGCACCCAGGCCTCCCTGCAGACTCCAATGGGGCCAGCACTGGAGGGGCCCCACCCACA
TGACTTTTCCATTGACCAGCTCTCTTCCCTGTCTTTGTTGTCTCCCTCTTTCTCAGTTTCTTTCTTTTCTAATT
CCTGTTGCTCTGTTTCTTCCCTTCTGTAGGTTTCTCTCTTCCCTTCTCCCTTCTCCCTTGCCTTCCCTTTCTCTC
TCCTATCCCCACGTCTGTCTCTCTTCTTATTCTGTGAGATGTTTTGTATTATTTACCAGCAGCATAGAACAGG
ACCTCTGCTTTTGCACACCTTTTCCCCAGGAGCAGAAGAGAGTGGGCCTGCCCTCTGCCCCATCATTGCACCTGC
AGGCTTAGGTCTCTCACTTCTGTCTCTTCTCAGAGCAAAAGACTTGAGCCATCCAAGAAACACTAAGCTCTC
TGGGCCTGGGTTCAGGGAAGGCTAAGCATGGCCTGGACTGACTGCAGCCCCCTATAGTCATGGGGTCCCTGCTG
CAAAGGACAGTGGCAGACCCCGGCAGTAGAGCCGAGATGCCTCCCCAAGACTGTCTATTGCCCTCCGATCGTGAG
GCCACCCACTGACCCAATGATCCTCTCCAGCAGCACACCTCAGCCCCACTGACACCCAGTGTCTTCCATCTTCA
CACTGGTTTGCCAGGCCAATGTTGCTGATGGCCCTCCAGCACACACATAAGCACTGAAATCACTTTACCTGC
AGGCACCATGCACCTCCCTTCCCTCCCTGAGGCAGGTGAGAACCCAGAGAGAGGGGCTGCAGGTGAGCAGGCAG
GGCTGGGCCAGGTCTCCGGGGAGGCAGGGGTCTGCAAGTCCGTGGTGGGTGAGCCAGCACCTCGCCCACTGGGA
GCTTCCCGGGATAAACTGAGCCTGTTTCACTTCTGATGTCCATTTGTCCCAATAGCTCTACTGCCCTCCCTTCCCC
TTTACTCAGCCAGCTGGCCACCTAGAAGTCTCCCTGCACAGCCTCTAGTGTCCGGGGACCTTGTGGGACCAGTC
CCACACCGCTGGTCCCTGCCCTCCCTGCTCCCAGGTTGAGGTGCGCTCACCTCAGAGCAGGGCCAAAGCACAGC
TGGGCATGCCATGTCTGAGCGGCGCAGAGCCCTCCAGGCCTGCAGGGGCAAGGGGCTGGCTGGAGTCTCAGAGCA
CAGAGGTAGGAGAACTGGGGTTCAAGCCCAGGCTTCCCTGGGTCCCTGCCTGGTCCCTCCCTCCCAAGGAGCCATTCT
ATGTGACTCTGGGTGGAAGTGCCAGCCCCCTGCCTGACGGXXXXXXGATCACTCTCTGCTGGCAGGATTCTTCC
CGCTCCCCACCTACCCAGCTGATGGGGGTGGGGTGTCTTTTTCAGCCAAGGCTATGAAGGGACAGCTGCTGGGA
CCCACCTCCCCCTTCCCCGGCCACATGCCGCGTCCCTGCCCCACCCGGGTCTGGTGTGAGGATACAGCTCTT
CTCAGTGTCTGAACAATCTCCAAAATTGAAATGTATATTTTTGCTAGGAGCCCCAGCTTCCCTGTGTTTTTAATAT
AAATAGTGTACACAGACTGACGAACTTTAAATAAATGGGAATTAATATTTAAAAAAAAGCGGCCCGCAATT
C

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FIGURE 32

MEQPQEEAPEVREEEEEKEEVAAEAGAPELNGGPQHALPSSSYTDLSRSSSPPSLLDQLQMGCDGASCGSLNMECR
VCGDKASGFHYGVHACEGCKGFFRRTIRMKLEYEKCERSCKIQKKNRNKCQYCRFQKCLALGMSHNAIRFGRMPE
AEKRKLVAGLTANEGSQYNPQVADLKAFSKHIYNAYLKNFNMTKKKARSILTGKASHTAPFVIHDIETLWQAEKG
LVWKQLVNGLPPYKEISVHVFYRCQCTTVETVRELTEFAKSIPSFSSFLNDQVTLLKYGVHEAIFAMLASIVNK
DGLLVANGSGFVTREFLRSLRKPFSDIIEPKFEFAVKFNALELDDSDLALFIAAIILCGDRPGLMNVPRVEAIQD
TILRALEFHLQANHPDAQYLFPKLLQKMADLRQLVTEHAQMMQRIKKTETETSLHPLLQEIKDMY

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FIGURE 33A

GGACACGGAGCCGCGAGGAGACAGCTGAGGCCCGCGGAGACCAGGGGGTGAAGCCTGGAGACCCTCTTGCCCTGG
CCTAGCTGCAGGCCCCCGGGATGCTTTGGGCATGTCTCTGGAGCCCCACAGAAGAGCAGCCCAATGGCCAGTGG
AGCTGAGGAGACCCAGGCTTCTTGACACGCTCCTGCAAGACTTCCCAGCCCTGCTGAACCCAGAGGACCCTCT
GCCATGGAAGGCCCCAGGGACGGTGCTCAGCCAGGAGGAGGTGGAGGGCGAGCTGGCTGAGCTGGCCATGGGCTT
TCTGGGCAGCAGGAAGGCCCGCCACCATTGCTGCTGCTCTGGCCCCACGAAGCAGTTTCACAGCTGCTACAGAC
AGACCTTTCCGAATTCAGGAAGTTGCCCAGGGAGGAAGAAGAAGAGGAGGAGGACGATGACGAGGAGGAAAAGGC
CCCTGTGACCTTGCTGGATGCCCAAAGCCTGGCACAGAGTTTCTTTAACCAGCTTTGGGAAGTCGCCGGCCAGTG
GCAGAAGCAGGTGCCATTGGCTGCCCGGGCTCACAGCGGCAGTGGCTGGTCTCCATCCACGCCATCCGGAACAC
TCGCCGCAAGATGGAGGACCGGCACGTGTCCCTCCCTTCCTTAACCAGCTCTTCGGCTTGTCTGACCCTGTGAA
CCGCGCCTACTTTGCTGTGTTTGTATGGTCACGGAGGCGTGGATGCTGCGAGGTACGCCGCTGTCCACGTGCACAC
CAACGCTGCCCCGCCAGCCAGAGCTGCCCCACAGACCCTGAGGGAGCCCTCAGAGAAGCCTTCCGGCGCACCCAGCA
GATGTTTCTCAGGAAAAGCCAAGCGAGAGCGGCTGCAGAGCGGCACCACAGGTGTGTGTGCGCTCATTGCAGGAGC
GACCCTGCACGTGCGCTGGCTCGGGGATTCCAGGTCATTTTGGTACAGCAGGGACAGGTGGTGAAGCTGATGGA
GCCACACAGACCAGAACGGCAGGATGAGAAGGCGCGCATTGAAGCATTGGGTGGCTTTGTGTCTCACATGGACTG
CTGGAGAGTCAACGGGACCCCTGGCCGCTCTCCAGAGCCATCGGGGATGTCTTCCAGAAGCCCTACGTGTCTGGGGA
GGCCGATGCAGCTTCCCGGGCGCTGACGGGCTCCGAGGACTACCTGCTGCTTGCCTGTGATGGCTTCTTTGACGT
CGTACCCACACAGGAAGTTGTTGGCCTGGTCCAGAGCCACCTGACCAGGCAGCAGGGCAGCGGGCTCCGTGTGCG
CGAGGAGCTGGTGGCTGCGGCCCGGGAGCGGGGCTCCACGACAACATCACGGTCATGGTGGTCTTCTCAGGGA
CCCCAAGAGCTGCTGGAGGGCGGGAACCAGGGAGAAGGGGACCCCCAGGCAGAAGGGAGGAGGCAGGACTTGCC
CTCCAGCCTTCCAGAACCTGAGACCCAGGCTCCACCAAGAAGCTTAGGTGTTTCCAGGCCCTGCCCTCCCTTC
CTCCCATCCTTGTCTTCTCTCCCTCAGAAGCCTCAGGACCCAAACAGGTGGCAGGCAGTGGACAGGGTGCCCCG
CCACAGTGCTTTCCCCAGCACCCAGAGCCAGTCGGGACACCCCCCGCAGCCGCTCCTGGTGGCTGTGGAAGTGC
ACTGGGTGGCGGGCAGATGGTGGAAAGGCAGCTTAGGAGACCTCACCAAAGAGAAGATGGACCGGCTCTTGCTCCC
AGCTCCTATTAGGCCCGGGGTGGGACCAGAGGTATAGGTGCCCAACGGCAGCCAAACCAAAGACACTGGTGTGC
ATGGGGCAGCATGGTTGTGACGTGGGACCCTGGGGCGGACCCAGGAGCCAAACTCTTGAAGCACCCCTGGGTG
AGGCCCAGCAGCGGAGTGGCCAGCCCCAGTTTCCCATTGCTCCTCTCTGCGGCCAGGGCCAGGTGGGTTTCATATT
TACAGATATGCCAGCCAGTCTTGGTGGCCACACCAGTGTCCCAAAGAGGAGAGCGCAGCAGAGCCAGGGGTCT
GTTCTGTAGCAGCCACCCCTGCCCCACTCCAGGGCAGCCATGATGTGCTTGGCCCACCAGGGCCTTCCGGGC
TGCTCTCTTCCCTGAGCCCGGAACCGGCGACGCACATGTGTCTTTTGGTGTGTTTGTTTTTTCCAGGGAGG
TCTAATTCCGAAGCAGTATTCCAGGTTTTCTCTTTGTTTTATCAGTGCCAAGATGACCTGTTGTGTATATAATT
TAAGCAGAGCTTAGCATTATTTTATTCTTTAGAAAACCTAAGTATTTACTTTTTTAAAGCTATTTTTCAAGGAA
CCTTTTTTTGCAGTATTATTGAATTTATTTTCTAAATCAGGATTGAAACAGGAACTTTTCCAGGTGGTGTAAATA
AGCCATTCAAGTGCCTTACACAGCTTTGAAGAACTAGGACTGCAGTGGGCTCGGATAGGCCCATGAGGTTTTT
AGAAAAGCAGGATTTGTTTTGTTAGGGAGGCATGATTTTGGTGAGATCTTTCTGGAAGAGTTTTCCGCCTCTTG
TGATGCTGAACACCCCCAAGGTTCTCCCTCCCCCGCTGCCAGGTGACTGGCAGGAGCTGCGACTGCCACGTA
GTGTTGCTGGGCCCCGACAGCGGGGCTCTGGGCATCCCGGGTGACCTTGGCCATCTGCCTGCATTCCACCCCC
TTGGGCCTGGCTGGATCCCAGGCAGAGGGACCTTGCTGCTGTGTGATTGGAACATTCCCAAATATCTTGTGAATT
TGTAATCAAAATTGGTCTCATTGGGAAAGACTCTTAATTAAGAGGCTCAGGCAAGCACAGAGGCAGCCCGTGGGTC
TCTGTCTCAGTCTGGAGGCAGCAGGGATGCTGCTGGGAGTCCATGGCACAGGCCACAGCCCTCACCTTGCCGCG
GTGGCTGGCAGCACGCCTGCCTTGTCTGCCCCATGCCCTGAACAGGCATGAGAGCTCCACGTCCCCTAGTGCAC
CCTGAGAGGGGGCTCACAAAGTGACCGATCCTGGGTGCCTCAGGGAGCTCACTGAGGGCGTGCAAAGTTGAAAGTG
GCAAGGCTGGGGGAGGGTGTGCGGTAGAGGGAAGAGGGCAGGGGGCTAGGGGAGGACTCAGAGGCCATCTGCAGG
GCCAAGCCACAGGAAGGGCTGAGCTGGAGGTGGGCAGGGCTGCTCCAGGCAGGTGAGAGCAGTGCAGGGGGAGGA
GAGGAGAAAGGGAGGAAGCTGGGCTGTGTGGTCCCCATGAAGGCATTGAGAGTCCACCTGCAGACAGCGAGAGCC
CCAGGAAGGTTTGACAGCTGTGCCCAAGCACCTTGGCTCCTCTCAGCTCGCCGAGGAGGCACGCTAGAGCCG
CCTTCCCGGTGGGAGCCCTCTGTCCACAGGGAGCGGGGAGCCAGCTTTGCTGGGGCCCTACCTGCATGCCCAGC
CTTACCCCTCATTCTCACAGCACAGATGAGGTTGAGACCATGCAGTCAATGCATTGCTTAAGGTCTCTTATTTAC
AAAAAAAACCTTAAACATAGTCGCTGTCAATTCAGACATTCAGAGAATGGTTGGCCACAAACAATGACCAAGTAT

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FIGURE 33B

TGCTTGGCTTAACTTGAAGGCCTGCTGTCTCCTTCTGGGGGTCAGGGACGCAGCTCCACCCTCACCCTAGCCCA
CCCTGCCCCGTGGGCATAACCTTGACGAAGAGAGAGAATGATTGGCATCTGCTTTTCTCTTTTCTTTGCTAATAAT
TCTGTTCCCTGGCTGCCGAGAGTGAAGTTTACCATGTGGAGGTTTGGCTCCTATCACCTGGTGGTCTGATTGATA
CCCTAGCCTGAGGCTCCACTGGAAGATCTCGCAGCCTCAGTGTATGGGAAACCCTTTCCCCAGGCTTGTCCCAGC
ACTGCCGCTCCCCACCCCTGAGCCAGGACCCAGAGGATGGCCATGCCCCGTGCCTGGCAGAGGTCTGGTGCCAG
CACTGGGAGCTGCTCCGCCCTTGCTTGGGGCCGAGGGAGCCCTCGTCCACCCTGCACAGCAGCTGGGCACAGA
GGAGCGCTCTTCCATCTTGACCAGGACTGCACCAAGAAGCACCAGGTGTCTTCAGCCTCCAACCTCCGGGGCGAC
CTTCTCTTCCAGCCACAGTCCCATGAGGGCCCTAGCCAGGGACACTGGTCTGTAAATTGTAATCCTTTCTCCAG
CCCAGCTCTCCACTTGTTCCCTTGTGTGAGCTGAGCAGGCAGTGCACCTCTGAGTGTCCCTTTTGTAAAGGCCAGG
GGTTGCACTGAGTCTGCAGAGGCCGCGACCTCCTAGAACGCTGTGGGTGCAAGTGAGCCGGCGTGTCTGGGGAG
ATGCTGCCAGCACACAGGGGCCCTCCTGCTGCCAGCAGGTTGGGGTGGTTAAGTCTTATTAGTGTCTATTCTTAA
AATTAAGTGGGCTGGAGAAGAATGGAGCTCCACATGCCAGCACCGTATATGGAATACAAAAGCTGGGGAAGCAGG
GCCTGCCTTACAGGTGTGGCTGACTCTGAGCCCAGGCCTGCAGGGGTGGAGGGCAGTCCCTCAGAATCCCAGAGG
CAGTCCCAGCCTCAGAACCCAGGATAGGAAATGGGTGTGTTTAGTGGGGAAAGGGACGGGGTGCAGACGGCAGGG
CCAGTATGGGGCCCCCTCCCTCTCCTCTCCTCTCCTATGGTGAGCCCAGCGTGGGCACCGGGCCGTCTCAGCCGT
GTTCCCAGGGCTGGGAGGACAGCTCTGGCCCTTCTTAGGCCTAGCCTCGTCCCAAGCTAAATGTAAGCCAGTTGG
GCTGTGTTAAAGGAAGCAGTGTGTTTGGTTTGATTCTGCCTCTGTAGCTCAAGGGGGGCAGCCCCAGAGTCTTG
TGCATTCTGCCAAGGCTCCATAGCTTTGCCAAATGCACGGAGCTCTGCCATTCCGGTGCAGTGCAGGCCTTGCGA
AGGGTTTATCTGCGTTCGTCTCGGTGGGCTTCTCCTGCATGGGAGTTGTGTTCTGTGCAAGGGGGAGCTTTGCT
CAGGACAGGATGACTGTCTTCCCTATTCTTAGGGACAAGTCCCAAGATGCCAGAAAGGCAGTCTCCCAAGGACCC
ACCATGCAGAAGTGTCAATAAACCAAGTTCTG

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FIGURE 34

MSSGAPQKSSPMASGAETPGFLDTLLQDFPALLNPEDPLPWKAPGTVLSQEEVEGELAEELAMGFLGSRKAPPP
AAALAHEAVSQLLQTDLSEFRKLPREEEEEEDDDEEEKAPVTLLDAQSLAQSFNRLWEVAGQWQKQVPLAARA
SQRQWLVSIIHAIRNTRRKMEDRHVSLPSFNQLFGLSDPVNRAYFAVFDGHGGVDAARYAAVHVHTNAARQPELPT
DPEGALREAFRRTDQMFLRKAKRERLQSGTTGVCALIAGATLHVAVLGD SQVILVQQGQVVKLMEPHRPERQDEK
ARIEALGGFVSHMDCWRVNGTLAVSRAIGDVFQKPYVSGEADAASRALTGSEDYLLACDGGFFDVVPHQEVVGLV
QSHLTRQQGSGLRVAEELVAAAARERGSHDNITVMVFLRDPQELLEGGNQEGDPQAEGRRQDLPSLPEPETQA
PPRS

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FIGURE 35

ATGCGGCGGCGCGTAGCGGCTCCACTCGCCGCCGGGGGTGAGGAGGCGGCAGCCACGACCTCCGTGCCCCGGGTCT
CCAGGTCTGCCGGGGAGACGCAGTGCAGAGCGGGCCCTAGAGGACGCCGTGGCCACCGGGACCCTGAACCTGTCT
AACC GGCGCTTGAAGCACTTCCCCCGGGGCGCGGCCCGTAGCTACGACCTGTCAGACATCACCCAGGCTGACCTG
TCCCGGAACCGGTTTCCCGAGGTGCCCGAGGCGGCGTGCCAGCTGGTGTCCCTGGAGGGCCTGAGCCTCTACCAC
AATTGCCTGAGATGCCTGAACCCAGCCTTGGGGAATCTCACAGCCCTCACCTACCTCAACCTCAGCCGAAACCAG
CTGTCGCTGCTGCCACCCTACATCTGCCAGCTGCCCTGAGGGTCCTCATCGTCAGCAACAACAAGCTGGGAGCC
CTGCCCCCTGACATCGGCACCCTGGGAAGCCTGCGACAGCTTGACGTGAGCAGCAACGAGCTCCAATCCCTGCCC
TCGGAACCTGTGTGGCCTCTCTTCCCTGCGGGACCTCAATGTCCGGAGGAACCAGCTCAGTACGCTGCCCCGAAGAG
CTGGGGGACCTCCCTCTGGTCCGCCTGGATTTCTCCTGTAACCGCGTCTCCCGAATCCCAGTCTCCTTCTGCCGC
CTGAGGCACCTGCAGGTCAATTCTGCTGGACAGCAACCCTCTGCAGAGTCCACCTGCCCAGGTCTGCCTGAAGGGG
AAACTTCACATCTTCAAGTATTTGTCCACAGAGGCCGGGCAGCGTGGGTGCGCCCTGGGGGACCTGGCCCCCTTCT
CGGCCCCCGAGTTTTCAGTCCCTGCCCTGCAGAGGATCTATTTCCGGGACATCGGTACGATGGTGGGCTGGACTCA
GGCTTCCACAGCGTTGATAGTGGCAGCAAGAGGTGGTCTGGAAATGAGTCAACAGATGAATTTTCAGAGCTGTCA
TTCCGGATCTCAGAGCTGGCCCCGGGAGCCCCGGGGGCCAGAGAACGCAAGGAGGATGGCTCAGCGGACGGAGAC
CCTGTGCAGATTGACTTCATCGACAGCCATGTCCCCGGGGAGGATGAAGAGCGAGGCACCTGTGGAGGAGCAGCGA
CCACCCGAATTAAGCCCTGGGGCAGGGGACAGGGAGAGGGCACCAAAACAGCAGGCGGGAGGAGCCGGCAGGGGAG
GAGCGGCGGCGCCCCGGACACCTTGCAGCTGTGGCAGGAGCGGGAACGGCGGCAGCAGCAGCAGAGCGGGGCGTGG
GGGGCCCCGAGGAAGGATAGCCTCTTGAAGCCAGGGCTCAGGGCTGTTGTGGGAGGGGGCCCGCCGCTGTCCACT
CAAGCCATGCACAACGGCTCGCCTAAGTCCAGTGCCTCCCAAGCAGGGGGCTGCAGCGGGGACAGGAGCCCCGCC
CCTGCCCCCTGCCTCCCAAGAGCCCCCTTCCCATAGCTGGACCAGCGACAGCACCTGCTCCACGGCCACTTGGCTCC
ATTTCAGAGACCAACAGCTTCTCTTCCGTTCTCCTCTCAGAGTGGCTCAGGCCCTTCTCACCAGACTCTGTCT
CTGAGACCTCGGCGGTACCCCCAGGTTCCAGATGAGAAGGACTTAATGACTCAGCTGCGCCAGGTCTTGTAGTCC
CGGCTGCAGCGGCCCCCTGCCTGAGGACCTGGCCGAGGCTCTGGCCAGTGGGGTATCCTGTGCCAGCTGGCCAAC
CAGCTACGGCCGCGCTCCGTGCCCTTCATCCATGTGCCCTCCCCCTGCTGTGCCAAAACCTCAGTGCCCTCAAGGCT
CGGAAGAATGTGGAGAGTTTTCTAGAAGCCTGTGAAAAATGGGGGTGCTGAGGCTGACCTGTGCTCGCCCCTCG
GATCTCCTCCAGGGCACTGCCCGGGGGCTGCGGACCGCGCTGGAGGCCGTGAAGCGGGTGGGGGGCAAGGCCCTA
CCGCCCCCTCTGGCCCCCTCTGGTCTGGGCGGCTTCGTGCTCTTCTACGTGGTCTCATGCTGCTGCTCTATGTC
ACCTACACTCGGCTCCTGGATCCCCGTTCCCCCAGGTGGCCTGGGAGGTGGCCCCCTCGAGGATGACTCCACTA
GCGCCCTGGGACCCCAAGTATGAAGCCAAAGCAGGACCTCGGCCGGTGTGGGTGAGTTGGGGGCAACCTGTGGG
ACTGGCTGGGGTGCTCAGGGAGCTGTGCGGTGGCCTGAGGCTCCAGTGCTCTGTCTCCTCACCTAGGGGGCCA
ACTGTAGCTCAGGAGCCTCGTTCTCAGGCCGGACGCTGTGTACCCCTCATTCTGGCCGCTGTATGAAGCAGCCT
CGGGCAGGGGTCTCAGGCCCGTGGCCCCCTGCCACAGGGCACTGGAATGGACAGCAGGCGCCCCCAGATGCAGGGT
TCCCGGTGGTGTGCTGTGAAGATGTCTTCTCTCGGACCCTCTGCTGCCCCGGGGGCAGCGTGTTCCTGTACC
TGTCCAAGGCCCCCAGCAGAT**TGA**TGGGCTCCCTGAAACTGCTGCCGCCGCCCCCATCATGTCTGCCAGGGTGC
TCCCCCGCCCATCACCTTCCCGGGGCCCTCCACTGCCTGGCTCAGCGGGCCGGAGCTGATCGCTCTCACTGGCC
TGCTGCAGATGAGCCAGGGGAGCCTAGGCCCAGCTCCTCCGCGGTTGGCCCCCAGACCATACTCTGACCCAC
CCAGCCCCCTGTGGTAGCCCCAGCAGTTCTCAGGGTGTGACCTCTCTCTCCACAGACCCAGACACCCATTGTC
CATAGCCTTCTCAGGGCAGAGTGGGCTGGTTGTGTTGACAATAAAACAGTGTGGTTTGCA

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FIGURE 36

MAAAVAAPLAAGGEEAAAATTSVPGSPGLPGRRSAERALEDVATGTINLSNRRLKHFPRGAARSYDLSDITQADL
SRNRFPEVPEAACQLVSLLEGLSLYHNCLRCLNPALGNLTALTYLNLSRNQLSLLPPYICQLPLRVLIVSNNKLGA
LPPDIGTLGSLRQLDVSSNELQSLPSELGCLSSLRDLNVRNQLSTLPEELGDLPLVRLDFSCNRVSRIPVSFCR
LRHLQVILLDSNPLQSPPAQVCLKGKLHIFKYLSTEAGQRGSALGDLAPSRPPSFSPCPAEDLFPGHRYDGGLDS
GFHSVDSGSKRWSGNESTDEFSELSFRISELAREPRGPRERKEDGSADGDPVQIDFIDSHVPGEDEERGTVVEEQR
PPELSPGAGDRERAPNSRREEPAGEERRRPDTLQLWQERERRQQQQSGAWGAPRKDSLKPKGLRAVVGAAAVST
QAMHNGSPKSSASQAGGCSGAGSPAPAPASQEPLPIAGPATAPAPRPLGSIQRPNSTFLFRSSSQSGSGPSSPDSV
LRPRYPQVPDEKDLMTQLRQVLESRLQRPLPEDLAEALASGVILCQLANQLRPRSVPFIVPSPAVPKLSALKA
RKNVESFLEACRKMGPVEADLCSPSDLLQGTARGLRTALEAVKRVGGKALPPLWPPSGLGGFVVVFYVVLMLLLLYV
TYTRLDPSPQVAVEVAPSRMTPLAPWDPKYEAKAGPRPVVWSWGQTCGTGWAQAGAVRWPEAPVLCPPHPRGP
TVAQEPRSQAGRCVTPHSGRCMKQPRAGVSGPWPLPQGTGMDSRPQMQGSRWCAVKMSSSRTLCCPGGSVFPCT
CPRPPSR

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FIGURE 37

GCGCGGCCCCATGTTCCTCCGCGCCGCGCTCGCCACCCCGCGGCCCCGCAGGATGAAGAAGGACGAGTCGTTCCCTG
GGCAAGCTGGGCGGCACCCTGGCCAGGAAGCGGAGGGCGCGGAGGTGAGTGACCTGCAGGAAGAAGGCAAGAAT
GCCATCAACTCACCAGATGTCCCCGCCCCTGGTGGATGTTACCCCTGAAGACACCCAGCTTGAGGAGAACGAGGAG
CGCACGATGATTGACCCCACTTCCAAGGAAGACCCCAAGTTCAAGGAACTGGTCAAGGTCCTCCTCGACTGGATT
AATGACGTGCTGGTGGAGGAGAGGATCATTGTGAAGCAGCTGGAGGAAGACCTGTATGACGGCCAGGTGCTGCAG
AAGCTCTTGAAAAAACTGGCAGGGTGCAAGCTGAATGTGGCTGAGGTGACACAGTCCGAAATAGGGCAGAAACAG
AAGCTGCAGACGGTGCTGGAAGCAGTACATGACCTGCTGCGGCCCCGAGGCTGGGCGCTCCGGTGGAGCGTGGAC
TCAATTCACGGGAAGAACCTGGTGGCCATCCTCCACCTGCTGGTCTCTCTGGCCATGCACTTCAGGGCCCCCATC
CGCCTTCCTGAGCATGTAACGGTGCAGGTGGTGGTGTGCGGAAACGGGAAGGCCTGCTGCATTCCAGCCACATC
TCGGAGGAGCTGACCACAACCTACAGAGATGATGATGGGCCGGTTCGAGCGGGATGCCTTCGACACGCTGTTTCGAC
CACGCCCCGGATAAGCTCAGCGTGGTGAAGAAGTCTCTCATCACTTTTGTGAACAAGCACCTGAACAAGCTGAAT
TTGGAGGTGACGGAACCTGGAGACCCAGTTTGAGATGGCGTGACCTGGTTCTGCTCATGGGCCTTCTGGAAGAC
TACTTTGTTCTCTCCACCACTTCTACCTGACTCCGGAAGCTTCGATCAGAAGGTCCACAATGTGTCCTTCGCC
TTTGAGCTGATGCTGGACGGAGGCCTCAAGAAACCAAGGCTCGTCCTGAAGACGTGGTTAACTTGGACCTCAA
TCCACCCTGAGGGTTCTTTACAACCTGTTTACCAAGTACAAGAACGTGGAGTTGACGGGGGAGCTGTGGATGGTGG
CAGGAGTGTCAGCAAGAAAGGCGGCATCCGTCTGTGCCCTGTGCCTTTCCAGGGAGCCAGGCGCCATGGGCTT
CTGGTCCAAGCTGTGTTGACTGTCATCCCCACCCACCCCTACCTCACGCCTGCCCCACCCCTGCCTCTTTTGG
TTGTTGTTCTTAATCTCCTCTCCATGTAGTTCCCAGTGGGCAAGAGCCTTTGAAAATGCAGGATTCTAAACACTC
GTGCTTGCGTTTGAAGCCTCGCGTCACTCAGTCGCGTGGGATGATGAGTCCGTTGTTGTCTGCCTTGGCCGAAAG
ATGAAAAAAAAGCCTGAACCCCAACCCCAAGCTGGTTGAGAGCACCTGCATTCTGCCTCATGGTGCAGTTAGCGA
TCACAGGCCTTCAGAAGTACAACATCAGCTCAGCAGGAACGCCGGCTCCCCGAGGACCCAGGCTTGACGATTCAC
CGGGGATCTCCTGGGCTGGGCTCTCCTTGGAAGTGAGGCCTTTTATTAAAAATAAAAGGGTTTTGCAGTTTGAAA
AAAAAAAAAAAAAAAAAAAAA

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FIGURE 38

MSSAPRSPTPRPRRMKKDESFLGKLGGLLARKRRAREVSDLQEEGKNAINSPMSPALVDVHPEDTQLEENEERTM
IDPTSKEDPKFKELVKVLLDWINDVLVEERIIVKQLEEDLYDGQVLQKLLEKLAGCKLNVAEVTQSEIGQKQKLO
TVLEAVHDLLRPRGWALRWSVDSIHGKNLVAILHLLVSLAMHFRAPIRLPEHVTVQVVVVRKREGLLHSSHISEE
LTTTTEMMGRFERDAFDTLFDHAPDKLSVVKKSLITFVNKHLNKNLEVTELETQFADGVYLVLLMGLLEDYFV
PLHHFYLTPESTFDQKVHNVSFAPFELMLDGGLKKPKARPEDVVNLDLKSTLRVLYNLFTKYKNVE

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FIGURE 39

GCTACGCGGGCCACGCTGCTGGCTGGCCTGACCTAGGCGCGCGGGGTCGGGCGGCCGCGCGGGCGGGCTGAGTGA
GCAAGACAAGACACTCAAGAAGAGCGAGCTGCGCCTGGGTCCCGGCCAGGCTTGACGCGAGAGGCGGGCGGCAGA
CGGTGCCCCGGCGGAATCTCCTGAGCTCCGCCGCCAGCTCTGGTGCCAGCGCCAGTGCCGCGCGCTTCGAAAAGT
GACTGGTGCCTCGCCGCCTCCTCTCGGTGCGGGACCATGAAGCTGCTGCCGTCGGTGGTGCTGAAGCTCTTTCTG
GCTGCAGTTCTCTCGGCACTGGTGACTGGCGAGAGCCTGGAGCGGCTTCGGAGAGGGCTAGCTGCTGGAACCAGC
AACCCGGACCCTCCCCTGTATCCACGGACCAGCTGCTACCCCTAGGAGGCGGCCGGGACCGGAAAAGTCCGTGAC
TTGCAAGAGGCAGATCTGGACCTTTTGAGAGTCACTTTATCCTCCAAGCCACAAGCACTGGCCACACCAAACAAG
GAGGAGCACGGGAAAAGAAGAAGAAAGGCAAGGGGCTAGGGAAGAAGAGGGACCCATGTCTTCGGAAATACAAG
GACTTCTGCATCCATGGAGAATGCAAATATGTGAAGGAGCTCCGGGCTCCCTCCTGCATCTGCCACCCGGGTAC
CATGGAGAGAGGTGTCTATGGGCTGAGCCTCCAGTGGAATAATCGCTTATATACCTATGACCACACAACCATCCTG
GCCGTGGTGGCTGTGGTGTCTGTCTGTCTGTCTGGTCACTCGTGGGCTTCTCATGTTTAGGTACCATAGG
AGAGGAGGTTATGATGTGGAATAATGAAGAGAAAGTGAAGTTGGGCATGACTAATTCCTCAAGAGAGACTTGTG
CTCAAGGAATCGGCTGGGACTGCTACCTCTGAGAAGACACAAGGTGATTTTCAAGTGCAGAGGGGAAAGACTTC
CATCTAGTCACAAAGACTCCTTCGTCCCCAGTTGCCGTCTAGGATTGGGCCTCCATAATTGCTTTGCCAAAATA
CCAGAGCCTTCAAGTGCCAAACAGAGTATGTCCGATGGTATCTGGGTAAAGAAGAAAGCAAAAGCAAGGGACCTTC
ATGCCCTTCTGATTCCCCTCCACCAAACCCCACTTCCCCTCATAAGTTTGTTTAAACACTTATCTTCTGGATTAG
AATGCCGTTTAAATTCCATATGCTCCAGGATCTTTGACTGAAAAAAAAAAGAAGAAGAAGAAGGAGAGCAAGAA
GGAAAGATTTGTGAAGTGAAGAAAGCAACAAAGATTGAGAAGCCATGTACTCAAGTACCACCAAGGGATCTGCC
ATTGGGACCCCTCCAGTGCTGGATTTGATGAGTTAACTGTGAAATACCACAAGCCTGAGAAGTGAATTTTGGGACT
TCTACCCAGATGGAAAAATAACAATAATTTTTGTTGTTGTTGTTTGTAAATGCCTCTTAAATTATATATTTATTT
TATTCTATGTATGTTAATTTATTTAGTTTTTAACAATCTAACAATAATATTTCAAGTGCCTAGACTGTTACTTTG
GCAATTTCTTGCCCTCCACTCCTCATCCCCACAATCTGGCTTAGTGCCACCCACCTTTGCCACAAAGCTAGGAT
GGTTCTGTGACCCATCTGTAGTAATTTATTGTCTGTCTACATTTCTGCAGATCTTCCGTGGTCAGAGTGCCACTG
CGGGAGCTCTGTATGGTCAGGATGTAGGGGTTAACTTGGTCAGAGCCACTCTATGAGTTGGACTTCAGTCTTGCC
TAGGCGATTTTGTCTACCATTTGTGTTTTGAAAGCCCAAGGTGCTGATGTCAAAGTGTAACAGATATCAGTGTCT
CCCCGTGTCCTCTCCCTGCCAAGTCTCAGAAGAGGTTGGGCTTCCATGCCTGTAGCTTTCCTGGTCCCTCACCCC
CATGGCCCCAGGCCACAGCGTGGGAACCTCACTTCCCTTGTGTCAAGACATTTCTCTAACTCCTGCCATTCTTCT
GGTGCTACTCCATGCAGGGGTCAGTGCAGCAGAGGACAGTCTGGAGAAGGTATTAGCAAAGCAAAAGGCTGAGAA
GGAACAGGGAACATTGGAGCTGACTGTTCTTGGTAACTGATTACCTGCCAATTGCTACCGAGAAGGTGGAGGTG
GGGAAGGCTTTGTATAATCCCACCCACCTACCAAAACGATGAAGGTATGCTGTCTATGGTCCTTTCTGGAAGTTT
CTGGTGCCATTTCTGAAGTGTACAACTTGTATTTCCAAACCTGGTTCATATTTATACTTTGCAATCCAAATAAA
GATAACCCTTATTCCATAAAAAAAAAAAAAAAAAA

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FIGURE 40

MKLLPSVVLKLF¹LA²AVLS³ALVTGESLERLRRGLAAGTSNPD⁴PPTVSTDQLLPLGGGRDRKVRDLQEADLDLLRVT
LSSKPQALATPNKEEHGKRKKKGKGLGKKRDPCLRKYKDFCIHGECKYVKELRAPSCICHPGYHGERCHGLSLPV
ENRLYTYDHTTILAVVAVVLSSVCLLVIVGLLMFRYHRRGGYDVENE⁵EKVKLGMTNSH

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FIGURE 41

ACGCGTCCGCTTCGGAATGAGAGACTCAACCATAATAGAAAAGAAATGGAGAACTATTAACCACCATTCTTCAGTGG
GCTGTGATTTTCAGAGGGGAATACTAAGAAATGGTTTTCCATACTGGAACCCAAAGGTAAAGACACTCAAGGACA
GACATTTTTTGGCAGAGCATAGATGAAAATGGCAAGTTCCCTGGCTTTCCTTCTGCTCAACTTTTCATGTCTCCCTC
TTCTTGGTCCAGCTGCTCACTCCTTGCTCAGCTCAGTTTTCTGTGCTTGGACCCTCTGGGCCCATCCTGGCCATG
GTGGGTGAAGACGCTGATCTGCCCTGTACCTGTTCCCGACCATGAGTGCAGAGACCATGGAGCTGAGGTGGGTG
AGTTCCAGCCTAAGGCAGGTGGTGAACGTGTATGCAGATGGAAAGGAAGTGAAGACAGGCAGAGTGCACCATAT
CGAGGGAGAACTTCGATTCTGCGGGATGGCATCACTGCAGGGAAGGCTGCTCTCCGAATACACAACGTACAGCC
TCTGACAGTGGAAAGTACTTGTGTTATTTCCAAGATGGTGACTTCTACGAAAAAGCCCTGGTGGAGCTGAAGGTT
GCAGCATTGGGTTCGATCTTCACATTGAAGTGAAGGGTTATGAGGATGGAGGGATCCATCTGGAGTGCAGGTCC
ACTGGCTGGTACCCCCAACCCCAATAAAGTGGAGCGACACCAAGGGAGAGAACATCCCGCTGTGGAAGCACCT
GTGGTTGCAGATGGAGTGGGCCTGTATGCAGTAGCAGCATCTGTGATCATGAGAGGCAGCTCTGGTGGGGGTGTA
TCCTGCATCATCAGAAATTCCCTCCTCGGCCCTGGAAAAGACAGCCAGCATACTCCATCGCAGACCCCTTCTTCAGG
AGCGCCAGCCCTGGATCGCGGCCCTGGCAGGGACCCTGCCTATCTCGTTGCTGCTTCTCGCAGGAGCCAGTTAC
TTCTTGTGGAGACAACAGAAGGAAAAAATTGCTCTGTCCAGGGAGACAGAAAGAGAGCGAGAGATGAAAGAAATG
GGATACGCTGCAACAGAGCAAGAAATAAGCCTAAGAGAGAAGCTCCAGGAGGAACCTCAAGTGGAGGAAAAATCCAG
TACATGGCTCGTGGAGAGAAGTCTTTGGCCTATCATGAATGGAAAATGGCCCTCTTCAAACCTGCGGATGTGATT
CTGGATCCAGACACGGCAAACGCCATCCTCCTTGTTTCTGAGGACCAGAGGAGTGTGCAGCGTGTGAAGAGCCG
CGGGATCTGCCAGACAACCCTGAGAGATTTGAATGGCGTTACTGTGTCCTTGGCTGTGAAAACCTTCACATCAGGG
AGACATTACTGGGAGGTGGAAGTGGGGGACAGAAAAGAGTGGCATATTGGGGTATGTAGTAAGAACGTGGAGAGG
AAAAAAGGTTGGGTCAAAATGACACCGGAGAACGGATACTGGACTATGGGCCTGACTGATGGGAATAAGTATCGG
GCTCTCACTGAGCCCAGAACCAACCTGAAACTTCTGAGCCTCCTAGGAAAGTGGGGATCTTCTGGAATATGAG
ACTGGAGAGATCTCGTTCTATAATGCCACAGATGGATCTCATATCTACACCTTTCGCGACGCCTCTTTCTCTGAG
CCTCTATATCCTGTTTTTCAGAATTTTGACCTTGGAGCCCACTGCCCTGACCATTGCCCCAATACCAAAAGAAGTA
GAGAGTTCCCCCGATCCTGACCTAGTGCCTGATCATTCCCTGGAGACACCACTGACCCCGGGCTTAGCTAATGAA
AGTGGGGAGCCTCAGGCTGAAGTAACATCTCTGCTTCTCCCTGCCACCCTGGAGCTGAGGTCTCCCTTCTGCA
ACAACCAATCAGAACCATAAAGCTACAGGCACGCACTGAAGCACTTTACTTGATATTCATTCCATTATTCCATATGA
CAGTTGTTTTGAGTTTCGTACCACCTTATTGTCCCCTTATACAGATAAGGAAACTGGGGTGCAGAAAGGTGAATT
AACTTTACAAAGTAGACATGACAAGTGAACAGCAGAGCTGGGATCTAAACAGCAATAACTAACATTAACAGAGAA
TTTAAATGTTCTTAGTGCTGTGTTATAAGCTTTGGTGGATGTCACTCCTTAAATCCTCACAACACCCTGTGCGG
TAGTCATATTTTGCAAGTATGGAAGCTGAGGCAGGGCAACATGAAGTAACTTACATAATTACATACAGTAATTTGT
GCAGTTGGGAGATGTTACAGCCTTAGTCCCTGGCTAATTGCCTGTTCTTTTCCAGCCTGATTTTTTTTCCCACAGG
AAGAGCCCACATGTAGCCCTGAGGTTTCTTCCCAGGACAGCTGCAGGGTAGAGATCATTTTAAAGTGCTTGTGGA
GTTGACATCCCTATTGACTCTTCCCAGCTGATATCAGAGACTTAGACCCAGCACTCCTTGGATTAGCTCTGCAG
AGTGTCTTGGTTGAGAGAATAACCTCATAGTACCAACATGACATGTGACTTGGAAGAGACTAGAGGCCACACTT
GATAAATCATGGGGCACAGATATGTTCCCACCCAACAAATGTGATAAGTGATTGTGCAGCCAGAGCCAGCCTTCC
TTCAATCAAGGTTTCCAGGCAGAGCAAATACCCTAGAGATTCTCTGTGATATAGGAAATTTGGATCAAGGAAGCT
AAAAAGAATTACAGGGATGTTTTTAATCCCACTATGGACTCAGTCTCCTGGAAATAGGTCTGTCCACTCCTGGTCA
TTGGTGGATGTTAAACCCATATTCTTTCAACTGCTGCCTGCTAGGGAAAAGTCTCCTCATTATCATCACTATT
ATTGCTCACCCTGTATCCCTCTACTTGGCAAGTGGTTGTCAAGTTCTAGTTGTTCAATAAATGTGTTAATAAT
GAAAAAAAAAAAA

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FIGURE 42

MKMASSSLAFLLLNFHVSFLVQLLTPCSAQFSVLGPSGPILAMVGEDADLPCHLFPTMSAETMELRWVSSSIRQV
VNVYADGKEVEDRQSAPYRGRTSILRDGITAGKAALRIHNVTASDSGKYLCYFQDGDIFYEKALVELKVAALGSDL
HIEVKGYEDGGIHLECRSTGWYPQPQIKWSDTKGENIPAVEAPVVADGVGLYAVAASVIMRGSSGGGVSCIIRNS
LLGLEKTASISIAADPFFRSAQPWIAALAGTLPISLLLLAGASYFLWRQQKEKIALSRETEREREMKEMGYAATEQ
EISLREKLQEELKWRKIQYMARGEKSLAYHEWKMALFKPADVILDPDTANAILLVSEDQRSVQRAEEPRLPDNP
ERFEWRYCVLGCENFTSGRHYWEVEVGDRKEWHIGVCSKNVERKKGWVKMTPENGYWTMGLTDGNKYRALTEPRT
NLKLPEPPRKVGIFLDYETGEISFYNATDGSHIYTFPHASFSEFLYPVFRILTLEPTALTICPIPKEVESSPDPD
LVPDHSLETPLTPGLANESGEPQAEVTSLLLPAHPGAEVSPSATTNQNHKLQARTEALY

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FIGURE 43

GGCACGAGGGTAGTGAGCGGTGTTTCAGGATGTGAGGGCCCGCAGGAGCCGAGTCAGGCTCTCTCCACTGCCTGC
CCGCCACCGTGCAAGCTCTGGCCGGCGCTGCCACAGTCCCCATGGTGGGCAGCCCCCGCGGGCGGGGACCCCTGA
TCGGCAGCGGC**ATG**CCAGGGAAGCCCAAGCACCTGGGCGTCCCCAACGGGCGCATGGTTCTGGCTGTGTCAGATG
GAGAGCTGAGCAGCACGACGGGGCCCCAGGGCCAGGGCGAGGGCCGCGCAGCTCTCTCAGCATCCACAGCCTCC
CCAGTGGTCCCAGCAGCCCCCTTCCCAACCGAGGAGCAGCCTGTGGCCAGCTGGGCCCTGTCTTCGAGCGGCTGT
TGCAGGACCCGCTGGGCCTGGCTTACTTCACTGAGTTCTGAAGAAGGAGTTCAGCGCGGAAAACGTGACTTTCT
GGAAGGCCTGCGAGCGCTTCCAGCAGATCCCGGCCAGCGATAACCAGCAGCTAGCTCAGGAGGCCCGCAACATCT
ACCAGGAGTTCTGTCCAGCCAGGCGCTGAGCCAGTGAACATCGACCGTCAGGCCTGGCTTGGCGAGGAGGTGC
TGGCCGAGCCCCGGCCGGACATGTTTCGGGCACAGCAGCTTCAGATCTTCAACTTGATGAAGTTCGACAGCTATG
CGCGCTTCGTCAAGTCCCCGCTGTACCGCGAGTGCCTGTAGCCGAAGCCGAGGGACGCCCTCTGCGGGAACCTG
GCTCCTCGCGCTCGGCAGCCCTGACGCCACGAGGAAGAAGCCGAAGCTGAAGCCCGGGAAGTCGTGCCGCTGG
GTGTGGAGGAGTTGGGGCAGCTGCCACCCGTTGAGGGTCTGGGGGCCGCCCTCTCCGCAAGTCTTCCGCCGGG
AGCTGGGCGGGACTGCAAACGCCGCCTTGCGCCGAGAGTCTCAGGGCTCCCTCAACTCCTCCGCCAGCCTGGACC
TTGGCTTCTAGCCTTCGTGAGCAGCAAATCTGAGAGCCACCGGAAGAGCCTTGGGAGCACGAGGGGTGAAAGTG
AAAGCCGGCCAGGGAAGTACTGCTGTGTGTACCTGCCCGATGGCACAGCCTCCTTGGCCCTGGCCAGACCTGGCC
TCACCATCCGAGACATGCTGGCAGGGATCTGTGAGAAAACGAGGCCTCTCTCTACCTGACATCAAGGTCTACCTGG
TGGGCAATGAACAGGCCCTGGTCTGGATCAGGACTGCACCGTGCTGGCGGATCAGGAAGTGC GGCTGGAAAAACA
GGATCACCTTCGAGCTGGAGCTGACGGCGCTGGAGCGCGTGGTACGAATCTCAGCCAAGCCCACCAAGCGGCTGC
AGGAGGCGCTGCAGCCCATTCTGGAGAAGCACGGCTTGAGCCCCGCTAGAGGTGGTGTGTCACCGGCCAGGCGAGA
AACAGCCTCTGGATCTGGGGAAGCTAGTGAGCTCGGTGGCGGCCAGAGACTGGTTTTGGACACTCTTCCAGGTG
TGAAGATCTCCAAAGCCCGTGACAAATCTCCCTGCCCGAGCCAGGGCTGCCACCTAGAACTCAGGATAAGGCCA
CCCATCCCCCTCCAGCGTCCCCCAGTTCTCTGGTGAAGGTGCCCAGTAGTGCCACTGGAAAGCGGCAGACCTGTG
ACATCGAAGGCCTGGTGGAGCTGCTGAACCGGGTGCAGAGCAGCGGGGCCACGACCAGAGGGGCCCTTCTGAGGA
AAGAGGACCTGGTACTTCCAGAATTTCTGCAGCTGCCCCGCCAAGGGCCAGCTCCGAGGAGACCCACACAGA
CCAAATCAGCAGCCAGCCCATCGGGGGATCCTTGAACCTCCACCACCGACTCAGCCCTC**TGAC**AGCTACCCAACA
GTCCAGGACAGCTGCATGGCACCCGGCGGGCCGAGCATGCCATGGGTCCGCTCTGCATGCCCTGTCTGTGCCATG
AGTGTCCCTGGCCCCCTTCTGCCATGGGCAGGCCCCGAGGAAGAGCCGGTAGGGGTGGAAAGGGGACTCAGATGA
GACACACCCACAGCTGCCACCGCCTTGTCCCTCAACAAGCTCACCCCAATCCCTTGACGCCAGGCCACAATGG
GGGAGGTGAGTCCAGCCCCTTGGAACAGGCTTGCCCAACATGGAGGGATGGCGTTGGCAGTGCCAGCCTCCCCAG
CCTGTGCCAAGCTTCAACAGGGGCAAGAGGAGGGGCCGCCCTCCTCAGGAAGCTGGTATGAGTAAGGCCTTGA
GGGTGCAGGCAGGCAGCCCTGTACCCACCCACATAGACTATACTGTACATACAGATTTTGCAGTAGGCTTGGGG
CAGCTGGGTTTGTCTTGATGTATGATACTGTTATTATAATAATTATTATTATTCTGCAAAAAAAAAAAAAAAAAA
AA

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FIGURE 44

MPGKPKHLGVPNGRMVLAVSDGELSSTTGPGQGEGRGSSLSIHSLSGSPSSPFPTEEQPVASWALSFERLLQDP
LGLAYFTEFLKKEFSAENVTFWKACERFQQIPASDTQQLAQEARNIYQEFLSSQALSPVNIDRQAWLGEEVLAEP
RPDMFRAQQQLQIFNLMKFDSYARFVKSPLYRECLLAEAEGRPLREPGSSRLGSPDATRKKPKLKP GKSLPLGVEE
LGQLPPVEGPGGRPLRKSFRELGGTANAALRRESQGS LNSSASLDLGFLAFVSSKSESHRKS LGSTEGESESRP
GKYCCVYLPDGTASLALARPGLTIRDMLAGICEKRGLSLPDIKVYLVGNEQALVLDQDCTVLADQEVRLNRI TF
ELELTALERVVRISAKPTKRLQEALQPILEKHGLSPLEVVLHRPGEKQPLDLGKLVSSVAAQRLVLDTLPGVKIS
KARDKSPCRSQGCPPTQDKATHPPASPSSLVKVPSSATGKRQTCDIEGLVELLN RVQSSGAHDQRGLLRKEDL
VLPEFLQLPAQGPSSEETPPQTKSAAQPIGGS LNSTTDSAL

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FIGURE 45

CCCCTGCCCGCCCGACAGCGCCGCGCCTGCCCCGCCATGGGTCGACAGAAGGAGCTGGTGTCCCGCTGCGGGGA
GATGCTCCACATCCGCTACCGGCTGCTCCGACAGGCGCTGGCCGAGTGCCTGGGGACCCCTCATCCTGGTGATGTT
TGGCTGTGGCTCCGTTGGCCAGGTTGTGCTCAGCCGGGGCACCCACGGTGGTTTTCTCACCATCAACCTGGCCTT
TGGCTTTGCTGTCACTCTGGGCATCCTCATCGCTGGCCAGGTCTCTGGGGCCACCTGAACCTGCCGTGACCTT
TGCCATGTGCTTCCTGGCTCGTGAGCCCTGGATCAAGCTGCCCATCTACACCCTGGCACAGACGCTGGGAGCCTT
CTTGGGTGCTGGAATAGTTTTTTGGGCTGTATTATGATGCAATCTGGCACTTCGCCGACAACCAGCTTTTTGTTTC
GGGCCCCAATGGCACAGCCGGCATCTTTGCTACCTACCCCTCTGGACACTTGGATATGATCAATGGCTTCTTTGA
CCAGTTCATAGGCACAGCCTCCCTTATCGTGTGTGTGCTGGCCATTGTTGACCCCTACAACAACCCCGTCCCCCG
AGGCCTGGAGGCCTTCACCGTGGGCCTGGTGGTCTGGTCAATTGGCACCTCCATGGGCTTCAACTCCGGCTATGC
CGTCAACCCTGCCCCGGGACTTTGGCCCCCGCCTTTTTACAGCCCTTGCGGGCTGGGGCTCTGCAGTCTTCACGAC
CGGCCAGCATTGGTGGTGGGTGCCCATCGTGTCCCCACTCCTGGGCTCCATTGCGGGTGTCTTCGTGTACCAGCT
GATGATCGGCTGCCACCTGGAGCAGCCCCACCCCTCCAACGAGGAAGAGAATGTGAAGCTGGCCCATGTGAAGCA
CAAGGAGCAGATCTTGAGTGGGCAGGGGCCATCTCCCCACTCCGCTGCCCTGGCCTTGAGCATCCACTGACTGTCC
AAGGGCCACTCCCAAGAAGCCCCCTTCACGATCCACCCTTTCAGGCTAAGGAGCTCCCTATCTACCCTCACCCCA
CGAGACAGCCCCCTCAGGATTTCCACTGGACCTTGCCCCAAATAGCACCTTAGGCCACTGCCCCTAAGCTGGGGTG
GAACCGGAATTTGGGTCAATACATCCTTTTGTCTCCCAAGGGAAGAGAATGGGCAGCAGGTATGTGTGTGTGTGC
ATGTGTGTGCATGTGTGTGCATGTGTGTGCAGGGGTGTGTGTGTGTGTGGGGGGGTTCAGATATTCAGGGCAAG
GGACCAGTCGGAAGGGATTCTGGCTATTGGGGGAGCCCAGAGACAGGGGAAGGCAGCCTGTCCATCTGTGCATAA
GGAGAGGAAAGTTCCAGGGTGTGTATGTTTCAGGGGCTTCACATGGAGGAGCTGCAGATAGATATGTGTTTCTGT
GTATGTGTATGTCTGCCTTTTTTTCTAAGTGGGGGCTTCTACAGGCTTTTGGGAAGTAGGGTGGATGTGGGTAGG
GCTGGGAGGAGGGGGCCACAGCTTAGGTTTGGAGCTCTGGATGTACATACATAAGTAGGAGCAGTGGGACGTGTT
TCTGTCTAATGCAGGCATGAAGGGTGGAGTGAAGTCAGGTCATAAGTTTCATGTTTGCTTTTGTTTTGTTTGT
TTTTAATGTATGTAGCAGATGTTACAGTCTTAGGGATCCGGGATGGGAGACCCCACTTTAGAAAGGGTCGTCAC
CCTTTAATCCTCTACTCAACAATGTACTCTTTTACTTTTATATTAAAAAAATAAAATAAATATGTGCCTAAAAA
AAAAAAAAA

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FIGURE 46

MGRQKELVSRGEMLHIRYRLLRQALAECLGTLILVMFGCGSVAQVVLSRGTHGGFLTINLAFGFAVTLGILIAG
QVSGAHLNPAVTFAMCFLAREPWIKLPIYTLAQTLGAFLGAGIVFGLYYDAIWHFADNQLFVSGPNGTAGIFATY
PSGHLDMINGFFDQFIGTASLIVCVLAIVDPYNNPVPRGLEAFTVGLVVLVIGTSMGFNSGYAVNPARDFGPRLF
TALAGWGS AVFTTGQHWWVP IVSPLLGSIAGVFVYQLMIGCHLEQPPPSNEEENVKLAHVKHKEQI

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FIGURE 47

TTTAGGTAAAACCGGATTTAAACCCTTGGGAAAAAAAAAAAAAAAAAGGAGAGAGAAGACAGTTCCTTTCTGTTAGAA
ATTAAAACAAAATACAAATTGAGGAAGCTCTGCTACCCAGGCTGTTCATGGTAGAGAACTTGAAGAAGACCTGTTT
GGATGGACACCTGGTTTTCAAAGTCAGGTGTGGAGACTGTTAAATGGGAGGGCCTCATCCATAAATGATTTCTGG
CAACGTCCTTCTCAGGTGGAGCTTGACGCTTTTTTAATGTTACTTGGGGAGGGAGTGCTCATTAAAGGGATGCCAG
GGCCAGCTCTGGTGGTTCCTGGGGAGGCTGCGTCCTTCCCTGCTTCTGCATGTCATGAGGCAGCAGGAAGGTTTC
CCCTGCACCTGTCTGTCCTGGCTCCCTCTGGGTAGCCCCCTACTGTTCTGTGCTTCAGCACAGCCTGGTTTGTCA
AGAGGCACATAGTTGGGGCTGGGCTGCATGGCACAGGGGCTTATGTGCCTGCTGGTTATTTAATTTTCAGCCTTA
AGTTTTCTTTAATATTTTCTGTTGGCTATTTAAAGGTTTGGTTATCTTTTATTCCTTATCTACAATCAAGATG
ACAATGTAATTGAATTATCTTATTTATAACACGGTTCGTGATTCATGATTCATGATTACAAGTAGAAAAATATGTC
ATGTTCCCTCACCTCCAAATAAATATGTGTGTGTCTGTNTGNGTGTCTATATGTATGTGCGGAGAGGGAGAGAGTG
GGGAAGGAGAGCAGTGTTATCATACATAGAGAGGCTAAATGTGTCCCATCCCTCACTGTCAGCTTTATAAAGGAG
TTTGACTCCATCCACAGAAGAATGTTTTATAAGACTAGGAAAAACAGTTGAAAACCTAGGATAAACAGCAACAAAA
ATCAACTAAATATGTTGTTACTGTTGCTAAGGATTTTCTCCTTAGAATAATTTAGGATTTTTAAAAATTTCTGTT
TGCCAAATGCTGTAGATAAATGGCCAGATTCTTCCATCCCTAGGATTCTTTATTATTTTTTTTTCACAGATTTT
GAGAACAAGGGGGAGAGATAGTATGGAAGATTAAGATTCCATTAATCTTATAGAAGTGTGTTGTACCCCAAATTC
CTGCTTGTGTTGAACATGGCATCTTCATAGATTACAGGATTCACCTACCCTCTATAGCTGGATCTTGAAAAATTATCTG
GCCAGATAATTTTGCATCTGCTTGGATGATTGTAGACTGAGATGTGAGTGGAGGATAAAGTATTAGACTTTTGTCT
GAGTAACTGCCAACCAAGAAGTATTTATCGGACACTTACTAGGTGCCTAGGATTGTATCAGAGGGAATATGAAAT
GTGTCCCTGCCCTACCTAGTTTTAAACGACAGAATATCTATTAAAGGCTACTTAGCTGAAGGGTAAGGGTGACAGG
TCTAGGGGAAGCTTTGGGAGGTGGTGTGCTGTGACAGAAAAAGTGGCAGAGTAGGGACGAGAGACCTGCATTCTA
GCCCTGTTTCTGTCACTTGCTCTGTACACTTAGACAACAGCTTGACCTCTTGAGCTTTAGTTTCTCCTCTGCAT
AATGAGAGGGTTAGACTACTGAATTGTATGGGAAAAAAAAATACAAATTCCTGGGTCTAGGCCATGCCTGCTGAAT
CCGACTGTTTCAGGAAGAGGCCTAGGAAATCTGTGAGGGAATCCCCAGGGGAATCTCGTGACCAGCCAGGTGTGAA
ATCTGCTAACTGGAAGATCTCAAAGCTTCCTTCACTTTTTGTGATTTTGTGGTCATGTAACGTTACTGTATTATT
CTACGTAAATGTGGGTACTTGGATGTTTATCATACTGTTTCTCTGTGTTTACATACTAATTTGTGTAAGAAATGC
ATTTTAGTCTGTGTACCTCAACCTGCTGTTTGTTCCTAGAGGTGTTAGTAGTCTTTAAATACAAGTAAGACTTA
AGAGGATATTTGATGTTATTTACCTGGATATTTCTTCCCTTTTATTTATTTAGAGGAAATTGAGATTCTAGGA
GCCAAAAAATGAAAAACAAATTTCTAAGGCAAAGTTAAAGAAAAAAATTACATTATTTCTTACCATTGCTACTT
TATAATGAAAATTTAAAAATTATATGGGAAGATTTTCTCTGGGATAACAAATCCTTGTCTATAAAGTAAGAGGTC
TTTTTAAAGTAGGTAGGCTATAAGGCCTGTAATTTAAAAATAATACTCCTTTCTCTAGGGTTTGGTGCAATTCCTC
ATTAATGAAGATAACATTTGAATTTCCCCAAAGCAGGTGAGGAGTCGGGGAGGAGAAAGCGATGTTAAAAATGAAAA
CTCACTGCAAAAGAGGAGGCAGAGGAAGAAGGAATGTAAACCCCTTAAAGCAGATGTGTGTGGGGCCTTATGAAG
ACCAGGATTCTGCGGGTGTGAGGGGATTGCCCTCTTGACAGAGACTAGGGTTTTAGACTGAGGCTTCCTGCAGG
GTGTTTCGCATTGCCCTTCTCCGTTCCCTTCAGACCTTTCTGGGGAGAAGAGGTGGGAGGAGGGGAGAAAGACTG
TTCATCTTATTCTGAATCCTGGAGCAGCTGAAGGTTTTCTCTTGAGTCAGGATGCAGTGGTAATGCATTAACCAG
CAAGTGTGGCCAAGGATAATGAAAAAGTGGGAAAGGAAGTCTCCTCCTCCTGATTGTAGCATCCAGCAGTCT
CTGTAGCCAGGTTACTCAAGAACCACATTTGATTTCTTGGCCCTTTGCCTTGGCAGTGATGGCATTTTTTATTTC
CTGTGTTTTAAAGTCTTCATTTATTTTTATAACATGGGTTAGGGAGAAGGGCCACAAATGGAGGGATTGTCTTTT
CAAGCACCACAGCTTCAGATAAAATTAGTACTTTCAAATATTGTCCACTTTAACTTAAAAAATTCTAGAGGGATT
ATATTGGAGACTCAACTGCCCTTGGTTTTAGTTTATAAAATGGCCTAGTACTGTGGAATTTTAAATTTTAGAAAGT
CTTAGCATCAGATCATAAACATTCATTAAAGAAGTCACATCCCATCTGAAACTTCCCAGGGGAGTTGGGATTCT
TAGTAGATTGGTAGAAAGGGGCTCATTTTCTACTGCATTTCCCATTTTTTGGTATCTTGTTCAGCATGTTTTATTT
TTATTTCTTGTCTGCAGAACATCCTATATTTATGAGAACATTCCTTAAGAAGACCACCACATAGAATACCCCTTC
CTATCAGCTCGCTCTGATTTAGCCTTAATTTGTAAATTTTTTAGAGATGAATGAAGTGCTGCTGTGGAAAGAA
ATGTACATATACTATTTCTGTATCATTAAATTTACATTTTTTATGGTTCAAG

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FIGURE 48

LGKTGFNPWEKKKKRREKTVPFL

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FIGURE 49A

CAGCCCCGAGCCCCGAGCCCCGAGCCGGCGCCACCGCGCCCCCGGCCATGGCTTTTGCCAATTTCCGCCGCA
TCCTGCGCCTGTCTACCTTCGAGAAGAGAAAGTCCCGCGAATATGAGCACGTCCGCCGCGACCTGGACCCCCAACG
AGGTGTGGGAGATCGTGGGCGAGCTGGGCGACGGCGCCTTCGGCAAGGTTTACAAGGCCAAGAATAAGGAGACGG
GTGCTTTGGCTGCGGCCAAAGTCATTGAAACCAAGAGTGAGGAGGAGCTGGAGGACTACATCGTGGAGATTGAGA
TCCTGGCCACCTGCGACCACCCCTACATTGTGAAGCTCCTGGGAGCCTACTATCACGACGGGAAGCTGTGGATCA
TGATTGAGTTCTGTCCAGGGGGAGCCGTGGACGCCATCATGCTGGAGCTGGACAGAGGCCTCACGGAGCCCCAGA
TACAGGTGGTTTGCCGCCAGATGCTAGAAGCCCTCAACTTCCTGCACAGCAAGAGGATCATCCACCGAGATCTGA
AAGCTGGCAACGTGCTGATGACCCTCGAGGGAGACATCAGGCTGGCTGACTTTGGTGTGTCTGCCAAGAATCTGA
AGACTCTACAGAAACGAGATTCTTCATCGGCACGCCTTACTGGATGGCCCCGAGGTGGTCATGTGTGAGACCA
TGAAAGACACGCCCTACGACTACAAAGCCGACATCTGGTCCCTGGGCATCACGCTGATTGAGATGGCCAGATCG
AGCCGCCACACCACGAGCTCAACCCCATGCGGGTCTGTCTAAAGATCGCCAAGTCAGACCCTCCACGCTGCTCA
CGCCCTCCAAGTGGTCTGTAGAGTTCCGTGACTTCTGAAGATAGCCCTGGATAAGAACCAGAAACCCGACCCA
GTGCCGCGCAGCTGCTGGAGCATCCCTTCGTGACGAGCATCACCAGTAACAAGGCTCTGCGGGAGCTGGTGGCTG
AGGCCAAGGCCGAGGTGATGGAAGAGATCGAAGACGGCCGGGATGAGGGGGAAGAGGAGGACGCCGTGGATGCCG
CCTCCACCCTGGAGAACCATACTCAGAACTCCTCTGAGGTGAGTCCGCCAAGCCTCAATGCTGACAAGCCTCTCG
AGGAGTCACCTTCCACCCCGCTGGCACCCAGCCAGTCTCAGGACAGTGTGAATGAGCCCTGCAGCCAGCCCTCTG
GGGACAGATCCCTCCAAACCACAGTCCCCCAGTCTGCGCCCTGGAAATGAGAACGGCCTGGCAGTGCCTGTGC
CCCTGCGGAAGTCCCGACCCGTGTCAATGGATGCCAGAATTCAGGTAGCCAGGAGAAGCAAGTTGCTGAGCAGG
GTGGGGACCTCAGCCAGCAGCCAACAGATCTCAAAGGCCAGCCAGAGCCGGCCCAACAGCAGCGCCCTGGAGA
CCTTGGGTGGGGAGAAGCTGGCCAATGGCAGCCTGGAGCCACCTGCCCAGGCAGCTCCAGGGCCTTCCAAGAGGG
ACTCGGACTGCAGCAGCCTCTGCACCTCTGAGAGCATGGACTATGGTACCAATCTCTCCACTGACCTGTCTGCTGA
ACAAAGAGATGGGCTCTCTGTCCATCAAGGACCCGAAACTGTACAAAAAACCTCAAGCGGACACGCAAAATTTG
TGGTGGATGGTGTGGAGGTGAGCATCACCACCTCCAAGATCATCAGCGAAGATGAGAAGAAGGATGAGGAGATGA
GATTTCTCAGGCGCCAGGAACCTCCGAGAGCTTCGGCTGCTCCAGAAAGAAGAGCATCGGAACCAGACCCAGCTGA
GTAACAAGCATGAGCTGCAGCTGGAGCAAATGCATAAACGTTTTGAACAGGAAATCAACGCCAAGAAGAAGTTCT
TTGACACGGAATTAGAGAACCTGGAGCGTCAGCAAAAGCAGCAAGTGGAGAAGATGGAGCAAGACCATGCCGTGC
GCCGCCGGGAGGAGGCCAGGCGGATCCGCCTGGAGCAGGATCGGGACTACACCAGGTTCCAAGAGCAGCTCAAAC
TGATGAAGAAAGAGGTGAAGAACGAGGTGGAGAAGCTCCCCGACAGCAGCGGAAGGAAAGCATGAAGCAGAAGA
TGGAGGAGCACACGCAGAAAAAGCAGCTTCTTGACCGGGACTTTGTAGCCAAGCAGAAGGAGGACCTGGAGCTGG
CCATGAAGAGGCTCACCACCGACAACAGGCGGGAGATCTGTGACAAGGAGCGCGAGTGCCTCATGAAGAAGCAGG
AGCTCCTTCGAGACCGGGAAGCAGCCCTGTGGGAGATGGAAGAGCACCAGCTGCAGGAGAGGCACCAGCTGGTGA
AGCAGCAGCTCAAAGACCAGTACTTCTCCAGCGGCACGAGCTGCTGCGCAAGCATGAGAAGGAGCGGGAGCAGA
TGCAGCGCTACAACCAGCGCATGATAGAGCAGCTGAAGGTGCGGCAGCAACAGGAAAAGGCGCGGCTGCCCAAGA
TCCAGAGGAGTGAGGGCAAGACGCGCATGGCCATGTACAAGAAGAGCCTCCACATCAACGGCGGGGGCAGCGCAG
CTGAGCAGCGTGAGAAGATCAAGCAGTTCTCCAGCAGGAGGAGAAGAGGCAGAAGTCGGAGCGGCTGCAGCAAC
AGCAGAAAACAGAGAACCAGATGCGGGACATGCTGGCGCAGTGTGAGAGCAACATGAGCGAGCTGCAGCAGCTGC
AGAATGAAAAGTGCCACCTCCTGGTAGAGCACGAAACCCAGAACTGAAGGCCCTGGATGAGAGCCATAACCAGA
ACCTGAAGGAATGGCGGGACAAGCTTCGGCCGCGCAAGAAGGCTCTGGAAGAGGATCTGAACCAGAAGAAGCGGG
AGCAGGAGATGTTCTTCAAGCTGAGCGAGGAGGCGGAGTGCCCCAACCCCTCCACCCCAAGCAAGGCCGCCAAGT
TCTTCCCCCTACAGTTCTGCGGATGCTTCTTAAACAACCGCCCCGGGGCTGTGGCTGGCAGCTTGGTGGGCCCCAGGG
CCTTCTCCTTCATTCTCTGTGAACATGTAACCTCAGGACCCCTTTTCCCTCTTGCGTCTGTGCCAGCTCAAATCCA
GCCCCCTCGCCCTGTGCCACCCCAACTGTGCCTGATAGACCTGCCCCAGCGTTCCTGACTTCTTGCTGGCCTGTGG
AGGGTGAGGTGTAATTATTTGTACCTGAACCTAATGTATATTCTCCTTGAGCCCCAGATCCCTTCAAGCTGGAA
GGGATGGGGCTGTTGGTGGGGTCAGGGTCCAAGAGGAATGGGTGTTCTGTGGCCTCGAGTCTCTCCTGTTTGCG
AAAATACCAGTTTTGCTCTCTGTGGGACAAAGCACTGCTGATGAAGTCCCGTGGGCTCATCCGGGCTGGAATTC
TTGGTTTTTCAGCCATTCCCTGCAGAGTCACTCAATCATCAAGTCCCTCACAGCCATTTCTGTTCCAGAGGAGC
CAGGCCTGCAGCTGGCTGCTCAGGAGATGGCCTCATTCCTCCTGTTCTCCAGTTTGCTTTCCACTTAAGACAAA
GCCTTGCTATGTGGGGGGCGGGGACCGGGGAAAGAGGGAGGCTGAAATGTTTATTCTGCTTCTCCCGTGTTTCA

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FIGURE 49B

TGCCATCTCGCGTCCCCCTTCCTGCACATGGGTGTGAATGCACACACATACGCGTACACACAGGACTTGGTCTGC
TGGCCTGGCCTCTTCTGCCCAGGTGGGTGGAAACACGTTTGCTGCCTGAGCCTGTGCCACTGAGCATGTTAGGTG
GAGCAGTTGGTGTGGCACGTGCGGGGTGTTGGCACCGGAGGCATGGAAAAGCACAGGCTGTACTGCCAGGCTGCG
ATGCGTGCTGGCCCCCGCACAGGCTCCTGTGTGCAGGGACTGATTCTCAGCACACGAGGCTTCACAACCCAGT
CTGCTCCATAGCACTCTGGCCCACCCTGTCTGCAGGTGAAACAGGAGGGCTGTTTGCCTCTGCCCCATCCCCCG
ACTGTGTTCAGGAGTCCACCTTGCAATTCAGACCTGGGCTGGCAGTCTGTTGGACTTCTCTTCAGGAAGAAAAA
GCATCAGGGGGAAATGGAATGCCCTGCCCCAGGAACATGGCAGAAGCACAGGTTCTGTACCTCAGATGGACTCC
TGCTGGGCCTTCGGGGTCTCAGTTGGCTTCCCCAGATTCTGATTCTACAGCTGCAGAATGTATATAACACAATA
AAAGCAAATGTTTGAACCAGT

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FIGURE 50

MAFANFRRILRLSTFEKRKSREYEHVRRDLDPNEVWEIVGELGDGAFGKVYKAKNKETGALAAKVIETKSEEEEL
EDYIVEIEILATCDHPYIVKLLGAYYHDGKLWIMIEFCPPGAVDAIMLELDRGLTEPQIQVVCROMLEALNFLHS
KRIIHRDLKAGNVLMTLEGDIRLADFGVSAKNLKTLQKRDSFIGTPYWMAPEVVMCETMKDTPYDYKADIWSLGI
TLIEMAQIEPPHHELNPMRVLLKIAKSDPPTLLTPSKWSVEFRDFLKIALDKNPETRPSAAQLLEHPFVSSITSN
KALRELVAEAKAEVMEEIEDGRDEGEEEDAVDAASTLENHTQNSSEVSPPSLNADKPLEESPSTPLAPSQSQDSV
NEPCSQPSGDRSLQTTSPPVVAPGNENGLAVPVPLRKSRPVSMDARIQVAQEKQVAEQGGDLSPAANRSQKASQS
RPNSSALETLGGEKLANGSLEPPAQAAPGPSKRDSDCSSLCTSESMDYGTNLSTDLSLNKEMGSLSIKDPKLYKK
TLKRTRKFVVDGVEVSITTSKIISEDEKKDEEMRFLRRQELRELRLLOKEEHRNQTQLSNKHELQLEQMHRFEQ
EINAKKKFFDTELENLERQQKQQVEKMEQDHAVRRREEARRIRLEQDRDYTRFQEQKLMKKEVKNEVEKLPRQQ
RKESMKQKMEEHTQKKQLLDRDFVAKQKEDLELAMKRLTTDNRRREICDKERECLMKKQELLRDREAALWEMEEHQ
LQERHQLVKQQLKDQYFLQRHELLRKHEKEREQMORYNQRMIEQLKVRQQQEKARLPKIQRSEGKTRMAMYKKS
HINGGGSAAEQREKIKQFSQQEEKRQKSERLQQQKQKHENQMRDMLAQCESNMSELQQLQNEKCHLLVEHETQKLK
ALDESHNQNLKEWRDKLRPRKKALEEDLNQKKREQEMFFKLSEEAECNPSTPSKAAKFFPYSSADAS

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FIGURE 51A

CATGTTGCCCTGGGGGGAACCTGCCAGCCCCGTAGCACTGCCCCACCCACCCACTGTGGTCTGTTGTACCCCACT
GCTGGGGTGGTGGTTCCAATGAGACAGGGCACACCAAACCTCCATCTGGCTGTTACTGAGGCGGAGACACGGGTGA
TGATTGGCTTTCTGGGGAGAGAGGAAGTCCTGTGATTGGCCAGATCTCTGGAGCTTGCCGACGCGGTGTGAGGAC
GCTCCACGAGGCCGGAATTGGCTGTGAAAGGACTGAGGCAGCCATCTGGGGGTAGCGGGCACTCTTATCAGAG
CGGCTGGAGCCGACCATCGTCCAGAGAGCTGGGGCAGGGGGCCGTGCCAATCTCCAGGGCTCCTGGGGCCAC
TGCTGACCTGGCTGGATGCATCGGGCAGTGGATCCTCCAGGGGCCGCTGCACGGAAGCCTTTGCCCTTGGG
GGCTGAGCTGTGCTGGGGCTGGAGCTCCTGCCCGCTCATCCCCCTCCTCGTAGCGCATGGCTGCCTGGAGGC
AGATGCTCAGCCAGCATTGGGCAGCCCCCGCTTCTGTCTCCCTACCCCTTCACATGGCAGTAGTTCTGGGCAC
CCCAGCAAACCATATTATGCTCCAGGGGCGCCCACTCCAAGACCCCTCCATGGGAAGCTGGAATCCCTGCATGGC
TGTGTGCAGGCATTGCTCCGGGAGCCAGCCAGCCAGGGCTTTGGGAACAGCTTGGGCAACTGTACGAGTCAGAG
CACGATAGTGAGGAGGCCACACGCTGCTACCACAGCGCCCTTCGATACGGAGGAAGCTTCGCTGAGCTGGGGCCC
CGCATTGGCCGACTGCAGCAGGCCAGCTCTGGAACCTTCATACTGGCTCCTGCCAGCACCGAGCCAAGGTCCTG
CCCCCACTGGAGCAAGTGTGGAACCTTGCTACACCTTGAGCACAAACGGAATATGGAGCCAAGCGGGGAGGTCCC
CCGGTGAAGCGAGCTGCTGAACCCCCAGTGGTGCAGCCTGTGCCTCCTGCAGCACTCTCAGGCCCCCTCAGGGGAG
GAGGGCCTCAGCCCTGGAGGCAAGCGAAGGAGAGGCTGCAACTCTGAACAGACTGGCCTTCCCCAGGGCTGCCA
CTGCCTCCACCACCATTACCACCACCACCACCACCACCACCACCACCCTGCCTGGCCTGGCTACCAGCCCCCA
TTTCAGCTAACCAAGCCAGGGCTGTGGAGTACCCTGCATGGAGATGCCTGGGGCCCAGAGCGCAAGGGTTACGA
CCCCCAGAGCGCCAGGAGCAGCGGCACTCGCTGCCTCACCCATATCCATACCCAGCTCCAGCGTACACCGCGCAC
CCCCCTGGCCACCGGCTGGTCCCGGCTGCTCCCCCAGGGCCAGGCCCCCGCCCCCAGGAGCAGAGAGCCATGGC
TGCTGCCTGCCACCCGTCCCCCGGAAGTGACCTTAGAGAGAGCAGAGTTAGAGGTCGCGGATGGACTCCAGC
GTTTCACCAGCAGCAACCACCGCCTGCGTGCCTTACGCCCCCTTCCCGGCCCTGGCCTCCCCGGCACCAACCACC
AGCAGCAGCAGTAGCAGCAGCAGCAACACTGGTCTCCGGGGCTGGAGCCGAACCCAGGCATTCCCGGCGCTGAC
CATTACCAAACCTCCCGCGCTGGAGGTCTCTCACCATGGCCGCTGGGGCCCTCGGCACACAGCAGTCGGAACCG
TTCTTGGGGGCTCCCGCTGCCACTCCCCACCTATCCCTGCCACCTGGACCTTCCTCACCCCTCCACCCCCCTGT
CCCCGCCTCTTACGCCCCCACCACCCCTGCCTGGTTGAAGGGTCCGGCCTGCCGGGCAGCCCCGAGAGGATGGA
GAGATCTTAGAAGAGCTCTTCTTTGGGACTGAGGGACCCCCCGCCCTGCCACCACCCCTCCCCCATCGCGAG
GGCTTCTTGGGGCTCCGGCCTCCCGCTTTTCTGTGGGCACTCAGGATTCTCACACCCCTCCCACTCCCCCAACC
CCAACCACCAGCAGTAGCAACAGCAACAGTGGCAGCCACAGCAGCAGCCCTGCTGGGCCTGTGTCTTTCCCCA
CCACCTATCTGGCCAGAAGTATAGACCCCTTCCCCGGCCTCCAGCCAGCACAGAACCCCAAGGACCCACCT
CTTGTAACCCCTGACTCTTGCCCTGCCTCCAGCCCTCCTTCCTCCTGCCACCAAAATACCTCAGGAAGCTTCAGG
CGCCCGGAGAGCCCCCGGCCAGGGTCTCCTTCCCAAAGACCCCGAGGTGGGGCCGGGGCCACCCCAAGGCCCC
CTGAGTAAAGCCCCCAGCCTGTGCCGCCCGGGGTGGGGAGCTGCCTGCCGAGGCCCTCGACTCTTTGATTTT
CCCCCACTCCGCTGGAGGACCAGTTTGAGGAGCCAGCCGAATTCAAGATCCTACCTGATGGGCTGGCCAACATC
ATGAAGATGCTGGACGAATCCATTGCAAGGAAGAGGAACAGCAACAACGAAGCAGGCGTGGCCCCCAACCC
CCGCTGAAGGAGCCCTTTGCATCTCTGCAGTCTCCTTTCCCCACCGACACAGCCCCCACCCTACTGCTCCTGCT
GTCGCCGTCACCACCACCACCACCACCACCACCACCACCGCCACCCAGGAAGAGGAGAAGAAGCCACCACCA
GCCCTACCACCACCACCGCCTCTAGCCAAGTTCCCTCCACCCTCTCAGCCACAGCCACCACCACCACCACCCCA
AGCCCCGCCAGCCTGCTCAAATCCTTGGCCTCCGTGCTGGAGGGACAAAAGTACTGTTATCGGGGGACTGGAGCA
GCTGTTTCCACCCGGCTGGGGCCTTGGCCACCACTCAGTATTCCCCTGGCCCCCATCAGGTGCTACCGCCCTG
CCGCCACCTCAGCGGCCCTAGCGCCAGGGCTCCCCACAGCCCTCTGCTTCTCGTCATCTCAGTTCTCTACC
TCAGGCGGGCCCTGGGCCCGGGAGCGCAGGGCGGGCGAAGAGCCAGTCCCGGGCCCCATGACCCCCACCAACCG
CCCCACCCCTATCTCTGCCCCCTGCTCGCTCTGAGTCTGAGGTGCTAGAAGAGATCAGCCGGGCTTGCGAGACC
CTTGTTGAGCGGGTGGGCCGGAGTGCCACTGACCCAGCCGACCCAGTGGACACAGCAGAGCCAGCGGACAGTGGG
ACTGAGCGACTGCTGCCCCCGCACAGGCCAAGGAGGAGGTGGCGGGGTGGCGGCAGTGTGAGGCAGCTGTAAG
CGGCGACAGAAGGAGCATCAGAAGGAGCATCGGCGGCACAGGCGGGCCTGTAAGGACAGTGTGGGTCTGCGGCC
CGTGAGGGCAGGGCAAAGGCCAAGGCCAAGGTCCCCAAAGAAAAGAGCCGCCGGGTGCTGGGGAACCTGGACCTG
CAGAGCGAGGAGATCCAGGGTCGTGAGAAGTCCCGGCCGATCTTGCGGGGCCTCCAAGGCCAAGCCACCCACA
GCTCCAGCCCCTCCATCAGCTCCTGCACCTTCTGCCAGCCACACCCCGTCAGCCTCTGTCCCTGGAAAGAAG

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FIGURE 51B

GCTCGGGAGGAAGCCCCAGGGCCACCGGGTGTGAGCCGGGCGGACATGCTGAAGCTGCGCTCACTTAGTGAGGGG
CCCCCAAGGAGCTGAAGATCCGGCTCATCAAGGTAGAGAGTGGTGACAAGGAGACCTTTATCGCCTCTGAGGTG
GAAGAGCGGCGGCTGCGCATGGCAGACCTCACCATCAGCCACTGTGCTGCTGACGTCGTGCGCGCCAGCAGGAAT
GCCAAGGTGAAAGGGAAGTTTCGAGAGTCTACCTTTCCCTGCCAGTCTGTGAAACCGAAGATCAACACTGAG
GAGAAGCTGCCCCGGGAAAACTCAACCCCCCTACACCCAGCATCTATCTGGAGAGCAAACGGGATGCCTTCTCA
CCTGTCTGCTGCAGTTCTGTACAGACCCTCGAAATCCCATCACAGTGATCCGGGGCCTGGCGGGCTCCCTGCGG
CTCAACTTGGGCCTCTTCTCCACCAAGACCCTGGTGGAAAGCGAGTGGCGAACACACCGTGGAAGTTCGCACCCAG
GTGCAGCAGCCCTCAGATGAGAACTGGGATCTGACAGGCACTCGGCAGATCTGGCCTTGTGAGAGCTCCCGTTCC
CACACCACCATTGCCAAGTACGCACAGTACCAGGCCTCATCCTTCCAGGAGTCTCTGCAGGAGGAGAAGGAGAGT
GAGGATGAGGAGTCAGAGGAGCCAGACAGCACCCTGGAACCCCTCCTAGCAGCGCACCAGACCCGAAGAACCAT
CACATCATCAAGTTTGGCACCAACATCGACTTGTCTGATGCTAAGCGGTGGAAGCCCCAGCTGCAGGAGCTGCTA
AAGCTGCCCCGCTTCATGCGGGTAACATCCACGGGCAACATGCTGAGCCACGTGGGCCACACCATCCTGGGCATG
AACACGGTGCAGCTGTACATGAAGGTGCCCGCAGCCGAACGCCAGGCCACCAGGAGAATAACAACCTTCTGCTCC
GTCAACATCAACATTGGCCCAGGCGACTGCGAGTGGTTTCGCGGTGCACGAGCACTACTGGGAGACCATCAGCGCT
TTCTGTGATCGGCACGGCGTGGACTACTTGACGGGTTCTGGTGGCCAATCCTGGATGATCTCTATGCATCCAAT
ATTCTGTGTACCGCTTCGTGCGAGCAGCCCGGAGACCTCGTGTGGATTAATGCGGGGACTGTGCACTGGGTGCAG
GCCACCGGCTGGTGAACAACATTGCCTGGAACGTGGGGCCCCCACCAGCCTATCAGTACCAGCTGGCCCTGGAA
CGATACGAGTGGAAATGAGGTGAAGAAGCTCAAATCCATCGTGCCCATGATTACGTGTATGGAACGTGGCTCGC
ACGGTCAAAATCAGCGACCCCGACTTGTTCAAGATGATCAAGTTCTGCCTGCTGCAGTCCATGAAGCACTGCCAG
GTGCAACGCGAGAGCCTGGTGCGGGCAGGGAAGAAAATCGCTTACCAGGGCCGTGTCAAGGACGAGCCAGCCTAC
TACTGCAACGAGTGCATGTGGAGGTGTTTAACATCCTGTTCTGTGACAAGTGAGAATGGCAGCCGCAACACGTAC
CTGGTACACTGCGAGGGCTGTGCCCGGCGCCGAGCGCAGGCCTGCAGGGCGTGGTGGTGTGAGCAGTACCGC
ACTGAGGAGCTGGCTCAGGCCTACGACGCCTTACGCTGGTGAAGGGCCCGCGGGCGCGCGGGCAGCGGAGGAGG
GCACTGGGGCAGGCTGCAGGGACGGGCTTCGGGAGCCCGGCCGCGCCTTTCCCTGAGCCCCCGCGGCTTTCTCC
CCCCAGGCCCCAGCCAGCACGTGCGATTGAGGGCCGGACGCCCCGCCCGCTGCCTGCCCGCGCAAGGCGCCGCGG
GGCCACCAGCACATGCCTGGGCTGGACCTAGGTCCCGCCTGTGGCCGAGAAGGGGGTGGGGCCAGCCCTTCCAC
CCCATTTGGCAGCTCCCCTCACTTAATTTATTAAGAAAACTTTTTTTTTTTTTTAGCAAATATGAGGAAAAAG
GAAAAAAATGGGAGACGGGGGAGGGGGCTGGCAGCCCTCGCCACCAGCGCTCCCCTCACCGACTTTGGCCT
TTTTAGCAACAGACACAAGGACCAGGCTCCGGCGGCGGCGGGGGTACATACGGGTTCCCTCACCCCTGCCAGCCG
CCCGCCCGCCGGCGCAGATGCACGCGGCTCGTGTATGTACATAGACGTTACGGCAGCCGAGGTTTTTAATGAGA
TTCTTTCTATGGGCTTTACCCCTCCCCCGGAACCTCCTTTTTTACTTCCAATGCTAGCTGTGACCCCTGTACATG
TCTCTTTATTCACTTGGTTATGATTTGTATTTTTTGTCTTTTCTTGTTTTTTGTTTTTTAATTTATAACAGTCC
CACTCACTCTATTTATTATTTTTTGGGAAAACCGACCTCCACACCCCCAAGCCATCCTGCCCCGCCCTCCAG
GGACCGCCCGTCGCGGGGCTCTCCCCGCGCCCCAGTGTGTGTCGGGGCCCGGCCGACCGTCTCCACCCGTCCGC
CCGCGGCTCCAGCCGGGTTCTCATGGTGTCAAACCCGCTCCCCCTCCCCTACGTCTGCACTTTCTCGGACCAGT
CCCCCACTCCCGACCCGACCCAGCCCCACCTGAGGGTGAGCAACTCCTGTACTGTAGGGGAAGAAGTGGGAAC
TGAAATGGTATTTTGTAAAAAAAATAAATAAAAATAAAAAAATTAAAGGTTTTAAAGAAAGAACTATGAGGAAAA
GGAACCCCGTCTTCCCAGCCCCGGCCAACCTTTAAAAAACACAGACCTTACCCCCACCCCTTTTCTTTTTTAAG
TGTGAAACAACCCAGGGCCAGGGCCTCACTGGGGCAGGGACACCCCGGGGTGAGTTTCTCTGGGGCTTTATTTTC
GTTTTGTGTGTTGTTTTTCTCCACGCTGGGGCTGCGGAGGGGTGGGGGGTTTACAGTCCCGCACCCCTCGCACTG
CACTGTCTCTGCCCCAGGGGCAGAGGGGTCTTCCCAACCCTACCCCTATTTTCGGTGATTTTTTGTGTGAGAAT
ATTAATATTAATAAATAAACGGAG

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FIGURE 52

GHPSKPYYPAGAPTFRPLHGKLESLHGCVQALLREPAQPGWLQGLQLYESEHDSEEATRCYHSALRYGGSFAEL
GPRIGRLQQAQLWNFHTGSCQHRKVLPPLEQVWNLLHLEHKRNYGAKRGPPVKRAAEPPVQPVPPAALSGPS
GEEGLSPGGKRRRRCNSEQTGLPPGLPLPPPPPLPPPPPPPPPPPPPPPLPGLATSPFFQLTKPGLWSTLHGDAWG
PERKGSAPPERQEQRHSLPHYPYPAPAYTAHPPGHRLVPAAPPGPGRPPGAESHGCLPATRPPGSDLRESRVQ
RSRMDSSVSPAATTACVPYAPSRPPGLPGTTTTSSSSSSSSSNTGLRGVEFPNPGIPGADHYQTPALEVSHHGRLGPS
AHSSRKPFLLGAPAAATPHLSLPPGPSSPPPPPCPRLLRPPPPPAWLKGPACRAAREDEGEILEELFFGTGEGPPRPAP
PPLPHREGFLGPPASRFSVGTQDSHTPTPTPTTTSSSNSNSGSHSSSSAGPVSFPPPPYLARSIDPLRPSPSA
QNPQDPPLVPLTLALPPAPPSSCHQNTSGSFRRPESPRPRVSFPKTPEVGP GPPPGPLSKAPQVPVPGVGELPAR
GPRLDFFPPTPLEDQFEPPAEFKILPDGLANIMKMLDESIRKEEEQQQHEAGVAPQPPLKEPFASLQSPFPDTDA
PTTTAPAVAVTTTTTTTTTTTTATQEEEEKKPPPALPPPPPLAKFPPPSQPQPPPPPPPPSPASLLKSLASVLEGQKY
CYRGTGAAVSTRPGPLPTTQYSPGPPSGATALPPTSAAPSAQGSPPQSASSSSQFSTSGGPWARERRAGEEPVPG
PMTPTQPPPPPLSLPPARSESEVLEEISRACETLVERVGRSATDPADPVDTAEPADSGTERLLPPAQAKEEAGGVA
AVSGSCKRRQKEHQKEHRRHRRACKDSVGRRPREGRAKAKAKVPKEKSRRVLGNLDLQSEEIQGREKSRPDLGGA
SKAKPPTAPAPPSAPAPSAQPTPPSASVPGKKAREEAPGPPGVSRADMLKLRLSLSEGPPKELKIRLIKVESGDKE
TFIASEVEERRLRMADLTISHCAADVVRASRNAKVKGKFRESYLSPAQSVKPKINTEEKLPREKLNPPTPSIYLE
SKRDAFSPVLLQFCTDPRNPITVIRGLAGSLRLNLGLFSTKTLVEASGEHTVEVRTQVQQPSDENWDLTGTRQIW
PCESSRSHTTIKAYAQYQASSFQESLQEEKESEDEESEEPDSTTGTPPSSAPDPKNHHIIKFGTNIDLSDAKRWK
PQLQELLKLPAFMRVTSTGNMLSHVGHTILGMNTVQLYMKVPGSRTPGHQENNNFCSVNINIGPGDCEWFVHEH
YWETISAFCDRHGVDYLTGSWWPILDDLYASNIPVYRFVQRPGLVWINAGTVHWVQATGWCNNIAWNVGPLTAY
QYQLALERYEWNEVKNVKSIVPMIHVSWNVARTVKISDPDLFKMIKFCLLQSMKHCQVQRESLVRAGKKIAYQGR
VKDEPAYYCNECDVEVFNILFVTSENGSRNTYLVHCEGCARRRSAGLQGVVLEQYRTEELAQAYDAFTLVRARR
ARGQRRRALGQAAGTGFGSPAAPFPEPPPAFSPQAPASTSR

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FIGURE 53A

ATGGGCGCCGCCGCCGCCGCCGTGCTGCCCGTGCTGCTGCTCCTGGCCGCCGCCGCCGCCCTGCCGGCGATGGGG
CTGCGAGCGGCCGCTGGGAGCCGCGCGTACCCGGCGGGACCCGCGCCTTCGCCCTCCGGCCCGGCTGTACCTAC
GCGGTGGGCGCCGCTTGACGCCCCGGGCGCCGCGGGAGCTGCTGGACGTGGGCCGCGATGGGCGGCTGGCAGGA
CGTCGGCGCGTCTCGGGCGCGGGGCGCCCGCTGCCGCTGCAAGTCCGCTTGGTGGCCCCGAGTGCCCCGACGGCG
CTGAGCCGCCGCTGCGGGCGCGACGACCTTCCCGGCTGCGGAGCCCGTGCCCGGCTCTGCGGAACCGGTGCC
CGGCTCTGCGGGGCGCTCTGCTTCCCGTCCCGGCGGCTGCGCGGCCGCGCAGCATTGCGCGCTCGCAGCTCCG
ACCACCTTACCCGCTGCCGCTGCCCGCGCGCCCCAGGCCCGCTGTCCCGGCCGTCCCATCTGCCTGCCGCCG
GGCGGCTCGGTCCGCTGCGTCTGCTGTGCGCCCTGCGGCGCGCGGCTGGCGCCGTCCGGGTGGGACTGGCGCTG
GAGGCCGCCACCGCGGGGACGCCCTCCGCGTCCCATCCCCATCGCCGCCCTGCCGCCGAACCTTGCCGAAGCC
CGGGCGGGGCCGCGGACGGGCCCGGGCGGGGACGAGCGGCAGAGGGAGCCTGAAGTTTCCGATGCCCAACTAC
CAGGTGGCGTTGTTTGAGAACGAACCGGCGGGCACCTCATCTCCAGCTGCACGCGCACTACACCATCGAGGGC
GAGGAGGAGCGCTGAGCTATTACATGGAGGGGCTGTTCGACGAGCGCTCCCGGGGCTACTTCCGAATCGACTCT
GCCACGGGCGCCGTGAGCACGACAGCGTACTGGACCGCGAGACCAAGGAGACGCACGTCTCAGGGTGAAAGCC
GTGGACTACGTACGCCGCCGCGCTCGGCCACCACCTACATCACTGTCTTGGTCAAAGACACCAACGACCACAGC
CCGGTCTTCGAGCAGTCGGAGTACCGCGAGCGCGTGCGGGAGAACCTGGAGGTGGGCTACGAGGTGCTGACCATC
CGCGCCAGCGACCGGACTCGCCCATCAACGCCAACTTGCCTTACCGCGTGTGGGGGGCGCGTGGGACGTCTTC
CAGCTCAACGAGAGCTCTGGCGTGGTGAGCACACGGGCGGTGCTGGACCGGAGGAGGCGGCCGAGTACCAGCTC
CTGGTGGAGGCCAACGACCAGGGGCGCAATCCGGGCCCGCTCAGTGCCACGGCCACCGTGTACATCGAGGTGGAG
GACGAGAACGACAACCTACCCCCAGTTTACGCGAGCAGAACTACGTGGTCCAGGTGCCCGAGGACGTGGGGCTCAAC
ACGGCTGTGCTGCGAGTGCAGGCCACGGACCGGGACCAGGGCCAGAACGCGGCCATTCACTACAGCATCCTCAGC
GGGAACGTGGCCGCCAGTTCTACCTGCACTCGCTGAGCGGGATCCTGGATGTGATCAACCCCTTGATTTCGAG
GATGTCCAGAAATACTCGCTGAGCATTAAAGGCCAGGATGGGGGCCGCCGCCCGCTCATCAATTCTTCAGGGGTG
GTGTCTGTGAGGTGCTGGATGTCAACGACAACGAGCCTATCTTTGTGAGCAGCCCCCTCCAGGCCACGGTGCTG
GAGAATGTGCCCTGGGCTACCCCGTGGTGACATTACAGCGGTGGACGCGGACTCTGGAGAGAACGCCCGGCTG
CACTATCGCCTGGTGGACACGGCCTCCACCTTTCTGGGGGGCGGCAGCGCTGGGCCTAAGAATCCTGCCCCACC
CCTGACTTCCCTTCCAGATCCACAACAGCTCCGGTTGGATCACAGTGTGTGCCGAGCTGGACCGCGAGGAGGTG
GAGCACTACAGCTTCGGGGTGGAGGCGGTGGACCACGGCTCGCCCCCATGAGCTCCTCCACCAGCGTGTCCATC
ACGGTGCTGGACGTGAATGACAACGACCCGGTGTTCACGCGAGCCACCTACGAGCTTCGTCTGAATGAGGATGCG
GCCGTGGGGAGCAGCGTGTGACCCTGCAGGCCCGGACCGTGACGCCAACAGTGTGATTACCTACCAGCTCACA
GGCGGCAACACCCGGAACCGCTTTGCACTCAGCAGCCAGAGAGGGGGCGGCCTCATCACCTGGCGCTACCTCTG
GACTACAAGCAGGAGCAGCAGTACGTGCTGGCGGTGACAGCATCCGACGGCACACGGTCGCACACTGCGCATGTC
CTAATCAACGTCACTGATGCCAACACCCACAGGCCTGTCTTTCAGAGCTCCCATTACACAGTGAGTGTCAGTGAG
GACAGGCCTGTGGGCACCTCCATTGCTACCCTCAGTGCCAACGATGAGGACACAGGAGAGAATGCCCGCATCACC
TACGTGATTACAGACCCCGTGCCGCACTTCGCGATTGACCCCGACAGTGGCACCATGTACACCATGATGGAGCTG
GACTATGAGAACCAGTTCGCTACACGCTGACCATCATGGCCCAGGACAACGGCATCCCGCAGAAATCAGACACC
ACCACCCTAGAGATCCTCATCCTCGATGCCAATGACAATGCACCCAGTTCTGTGGGATTTCTACCAGGGTTCC
ATCTTTGAGGATGTCTCCACCCTCGACCAGCATCCTCCAGGTCTCTGCCACGGACCGGGACTCAGGTCCCAATGGG
CGTCTGCTGTACACCTTCCAGGGTGGGGACGACGGCGATGGGGACTTCTACATCGAGCCCACGTCCGGTGTGATT
CGCACCCAGCGCCGGCTGGACCGGGAGAATGTGGCCGTGTACAACCTTTGGGCTCTGGCTGTGGATCGGGGCAGT
CCCCTCCCTTAGCGCCTCGGTAGAAAATCCAGGTGACCATCTTGGACATTAATGACAATGCCCCATGTTTGGAG
AAGGACGAACTGGAGCTGTTTGTGAGGAGAAACAACCCAGTGGGGTCGGTGGTGGCAAAGATTCTGTCTAACGAC
CCTGATGAAGGCCCTAATGCCCAGATCATGTATCAGATTGTGGAAGGGGACATGCGGCATTTCTTCCAGCTGGAC
CTGCTCAACGGGGACCTGCGTGCCATGGTGGAGCTGGACTTTGAGGTCCGGCGGGAGTATGTGCTGGTGGTGCAG
GCCAGTTCGGCTCCGCTGGTGAGCCGAGCCACGGTGACATCCTTCTCGTGGACCAGAATGACAACCCGCTGTG
CTGCCCCACTTCCAGATCCTCTTCAACAATAATGTACCAACAAGTCCAACAGTTTCCCCACCGGCGTGATCGGC
TGCATCCCGGCCATGACCCCGACGTGTGAGACAGCTCAACTACACCTTCGTGAGGGCAACGAGCTGCGCCTG
TTGTGCTGGACCCCGCCACGGGCGAACTGCAGCTCAGCCGCGACCTGGACAACAACCGGCCGCTGGAGGCGCTC
ATGGAGGTGCTGTGTCTGATGGCATCCACAGCGTCACGGCCTTCTGCACCCTGCGTGTACCATCATCACGGAC

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FIGURE 53B

GACATGCTGACCAACAGCATCACTGTCCGCTGGAGAACATGTCCCAGGAGAAGTTCTGTCCCCGCTGCTGGCC
CTCTTCGTGGAGGGGGTGGCCGCCGTGCTGTCCACCACCAAGGACGACGTCTTCGTCTTCAACGTCCAGAACGAC
ACCGACGTGAGCTCCAACATCCTGAACGTGACCTTCTCGGCGCTGCTGCCTGGCGGCGTCCGCGGCCAGTTCTTC
CCGTGCGAGGACCTGCAGGAGCAGATCTACCTGAATCGGACGCTGCTGACCACCATCTCCACGCAGCGCGTGCTG
CCCTTCGACGACAACATCTGCCTGCGCGAGCCCTGCGAGAACTACATGAAGTGCGTGCTCCGTTCTGCGATTTCGAC
AGCTCCGCGCCCTTCCTCAGCTCCACCACCGTGCTCTTCGGGCCATCCACCCCATCAACGGCCTGCGCTGCCGC
TGCCCGCCGGCTTCACCGGCGACTACTGCGAGACGGAGATCGACCTCTGCTACTCCGACCCGTGCGGCGCCAAC
GGCCGCTGCCGAGCCGCGAGGGCGGCTACACCTGCGAGTGCTTCGAGGACTTCACTGGAGAGCACTGTGAGGTG
GATGCCCGCTCAGGCCGCTGTGCCAACGGGGTGTGCAAGAACGGGGGCACCTGCGTGAACCTGCTCATCGGCGGC
TTCCACTGCGTGCTCTCTGCGAGTATGAGAGGCCCTACTGTGAGGTGACCACCAGGAGCTTCCGCCCCAG
TCCTTCGTACCTTCCGGGGCCTGAGACAGCGCTTCCACTTCACCATCTCCCTCACGTTTGCCACTCAGGAAAGG
AACGGCTTGCTTCTCTACAACGGCCGCTTCAATGAGAAGCAGCACTTCATCGCCCTGGAGATCGTGGACGAGCAG
GTGCAGCTCACCTTCTCTGAGGCGAGACAACAACGACCGTGGCACCAGAAGGTTCCAGTGGTGTGAGTGACGGG
CGGTGGCACTCTGTGCAGGTGCAGTACTACAACAAGCCCAATATTGGCCACCTGGGCCTGCCCCATGGGCCGTCC
GGGGAAGATGGCCGTGGTGACAGTGGATGATTGTGACACAACCATGGCTGTGCGCTTTGGAAAGGACATCGGG
AACTACAGCTGCGCTGCCAGGGCACTCAGACCGGCTCCAAGAAGTCCCTGGATCTGACCGGCCCTCTACTCCTG
GGGGGTGTCCCAACCTGCCAGAAGACTTCCAGTGACACAACCGGCAGTTCGTGGGCTGCATGCGGAACCTGTCA
GTCGACGGCAAAAATGTGGACATGGCCGATTTCATCGCCAACAATGGCACCCGGGAAGGCTGCGCTGCTCGGAGG
AACTTCTGCGATGGGAGGCGGTGTGAGAATGGAGGCACCTGTGTCAACAGGTGGAATATGTATCTGTGTGAGTGT
CCACTCCGATTTCGGCGGGAAGAAGTGTGAGCAAGCCATGCCTCACCCCCAGCTCTTCAGCGGTGAGAGCGTCGTG
TCCTGGAGTGACCTGAACATCATCATCTCTGTGCCCTGGTACCTGGGGCTCATGTTCCGGACCCGGAAGGAGGAC
AGCGTTCTGATGGAGGCCACCAGTGGTGGGCCACCAGCTTTCGCTCCAGATCCTGAACAACCTACCTCCAGTTT
GAGGTGTCCACGGCCCTCCGATGTGGAGTCCGTGATGCTGTCCGGGTTGCGGGTGACCGACGGGGAGTGGCAC
CACCTGCTGATCGAGCTGAAGAATGTTAAGGAGGACAGTGAGATGAAGCACCTGGTACCATGACCTTGACTAT
GGGATGGACCAGAACAAGGCAGATATCGGGGGCATGCTTCCCGGGCTGACGGTAAGGAGCGTGGTGGTCCGAGGC
GCCTCTGAAGACAAGGTCTCCGTGCGCCGTGGATTCCGAGGCTGCATGCAGGGAGTGAGGATGGGGGGGACGCCC
ACCAACGTGCCCACCTGAACATGAACAACGCACTCAAGGTGAGGTGAAGGACGGCTGTGATGTGGACGACCCC
TGTACCTCGAGCCCTGTCCCCCAATAGCCGCTGCCACGACGCTGGGAGGACTACAGCTGCGTCTGTGACAAA
GGGTACCTTGGAATAAACTGTGTGGATGCCTGTACCTGAACCCCTGCGAGAACATGGGGGCTGCGTGCGCTCC
CCCGGCTCCCCGAGGGCTACGTGTGCGAGTGTGGGCCAGTCACTACGGGCCGTACTGTGAGAACAACTCGAC
CTTCCGTGCCCCAGAGGCTGGTGGGGGAACCCCGTCTGTGGACCTGCCACTGTGCCGTGAGCAAGGCTTTGAT
CCCGACTGTAATAAGACCAACGGCCAGTGCCAATGCAAGGAGAATTACTACAAGCTCCTAGCCCAGGACACCTGT
CTGCCCTGCGACTGCTTCCCCATGGCTCCACAGCCGCACTTGCGACATGGCCACCGGGCAGTGTGCTGCAAG
CCCGGCGTATCGGCCGCAAGTGAACCGCTGCGACAACCCGTTTGCCGAGGTACACACGCTCGGCTGTGAAGTG
ATCTACAATGGCTGTCCCAAAGCATTTGAGGCCGGCATCTGGTGGCCACAGACCAAGTTTCGGGCAGCCGGCTGCG
GTGCCATGCCCTAAGGGATCCGTTGGAAATGCGGTCCGACACTGCAGCGGGGAGAAGGGCTGGCTGCCCCCAGAG
CTCTTTAACTGTACCACCATCTCCTTCGTGGACCTCAGGGCCATGAATGAGAAGCTGAGCCGCAATGAGACGCAG
GTGGACGGCGCCAGGGCCCTGCAGCTGGTGGGGCGCTGCGCAGTGCTACACAGCACACGGGCACGCTCTTTGGC
AATGACGTGCGCACGGCCTACCAGCTGCTGGGCCAGTCTTTCAGCACGAGAGCTGGCAGCAGGGCTTCGACCTG
GCAGCCACGCAGGACGCCGACTTTCACGAGGACGTTCATCCACTCGGGCAGCGCCCTCCTGGCCCCAGCCACCAGG
GCGGCGTGGGAGCAGATCCAGCGGAGCGAGGGCGGCACGGCACAGCTGCTCCGGCGCCTCGAGGGCTACTTCAGC
AACGTGGCACGCAACGTGCGGCGGACGTACCTGCGGCCCTTCGTATCGTACCGCCAACATGATTCTTGCTGTC
GACATCTTTGACAAGTTCAACTTTACGGGAGCCAGGGTCCCGCGATTTCGACACCATCCATGAAGAGTTCCCCAGG
GAGCTGGAGTCTCTCGTCTCCTTCCAGCCGACTTCTTCAGACCACCTGAAGAAAAGAAGGCCCCCTGCTGAGG
CCGGCTGGCCGAGGACCACCCCGCAGACCACGCGCCCGGGGCTGGCACCAGAGGGGAGGCCCCGATCAGCAGG
CGGAGGCGACACCCTGATGACGCTGGCCAGTTCGCCGTGCTCTGGTTCATCATTTACCGCACCCCTGGGGCAGCTC
CTGCCCCAGCGCTACGACCCCGACCGTGCAGCCTCCGTTGCCTCACCGGCCCATCATTAATACCCCGATGGTG
AGCACGCTGGTGTACAGCGAGGGGGCTCCGCTCCCGAGACCCCTGGAGAGGGCCGCTCCTGGTGGAGTTCGCCCTG

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FIGURE 53C

CTGGAGGTGGAGGAGCGAACCAAGCCTGTCTGCGTGTTCCTGGAACCACTCCCTGGCCGTTGGTGGGACGGGAGGG
TGGTCTGCCCCGGGGCTGCGAGCTCCTGTCCAGGAACCGGACACATGTGCGCTGCCAGTGCAGCCACACAGCCAGC
TTTGCGGTGCTCATGGATATCTCCAGGCGTGAGAACGGGGAGGTCCTGCCTCTGAAGATTGTCACCTATGCCGCT
GTGTCTTGTCACTGGCAGCCCTGCTGGTGGCCTTCGTCTCTCTCAGCTGGTGTTCGTGATTGGGATCAACCAGACG
CACAGCATTACAAAGCACCTCGCCGTGGCGCTCTTCCTCTCTCAGCTGGTGTTCGTGATTGGGATCAACCAGACG
GAAAACCCGTTTCTGTGCACAGTGGTTGCCATCCTCCTCCACTACATCTACATGAGCACCTTTGCCTGGACCCTC
GTGGAGAGCCTGCATGTCTACCGCATGCTGACCGAGGTGCGCAACATCGACACGGGGCCCATGCGGTTCTACTAC
GTCGTGGGCTGGGGCATCCCGGCCATTGTACAGGACTGGCGGTGCGCCTGGACCCCAGGGCTACGGGAACCCC
GACTTCTGCTGGCTGTGCGTTCAAGACACCCTGATTTGGAGCTTTGCGGGGCCATCGGAGCTGTTATAATCATC
AACACAGTCACTTCTGTCTATCTGCAAAGGTTTCTGCCAAAGAAAGCACATTATTATGGGAAAAAAGGGATC
GTCTCCCTGCTGAGGACCGCATTCTCTGCTGCTGCTCATCAGCGCCACCTGGCTGCTGGGGCTGCTGGCTGTG
AACC CGATGCACTGAGCTTTCACTACCTCTTCGCCATCTTCAGCGGCTTACAGGGCCCCCTTCGTCTCTCTTTTC
CACTGCGTGTCAACCAGGAGGTCCGGAAGCACCTGAAGGGCGTGCTCGGCGGGAGGAAGCTGCACCTGGAGGAC
TCCGCCACCACCAGGGCCACCCTGCTGACGCGCTCCCTCAACTGCAACACCACCTTCGGTGACGGGCTGACATG
CTGCGCACAGACTTGGGCGAGTCCACCGCCTCGCTGGACAGCATCGTCAGGGATGAAGGGATCCAGAAGCTCGGC
GTGTCTCTGGGCTGGTGAGGGGCAGCCACGGAGAGCCAGACGCGTCCCTCATGCCCAGGAGCTGCAAGGATCCC
CCTGGCCACGATTCCGACTCAGATAGCGAGCTGTCCCTGGATGAGCAGAGCAGCTCTTACGCCTCTCACACTCG
TCAGACAGCGAGGACGATGGGGTGGGAGCTGAGGAAAAATGGGACCCGGCCAGGGGCGCCGTCCACAGCACCCCC
AAAGGGGACGCTGTGGCCAACCACGTTCCGGCCGGCTGGCCCGACCAGAGCCTGGCTGAGAGTGACAGTGAGGAC
CCCAGCGGCAAGCCCCGCTGAAGGTGGAGACCAAGGTGACGCTGGAGCTGCACCGCGAGGAGCAGGGCAGTCAC
CGTGAGAGTACCCCCCGGACCAGGAGAGCGGGGGCGCAGCCAGGCTTGCTAGCAGCCAGCCCCAGAGCAGAGG
AAAGGCATCTTGAAAAATAAAGTCACCTACCCGCCCGCTGACGCTGACGGAGCAGACGCTGAAGGGCCGGCTC
CGGGAGAAGCTGGCCGACTGTGAGCAGAGCCCCACATCCTCGCGACGCTCTTCCTGGGCTCTGGCGGGCCCCGAC
TGCGCCATCACAGTCAAGAGCCCTGGGAGGGAGCCGGGGCGTGACCACCTCAACGGGGTGGCCATGAATGTGCGC
ACTGGGAGCGCCCAGGCCGATGGCTCCGACTCTGAGAAACCGTGAGGCAAGCCCGTCACCCACACAGGCTGCGG
CATCACCTCAGACCTTGAGGCCAAGGGGCCACTGCCCTTGAAGTGGAGTGGGCCAGAGTGTGGCGGTCCCCA
TGGTGGCAGCCCCCGACTGATCATCCAGACACAAAGGTCTTGTTCTCCAGGAGCTCAGGGCCTGTGACACCT
GGTGACAAGTGCCAAAGGCCACAGGCATGAGGGAGGCGTGACCCTGGGCCAGCACCGCTGAGTCCTAAGACTG
CAGTCAAAGCCAGAAGTGAAGGGGACCCAGACTGGGCCAGAGGCTGGCCAGAGTTGAGGAACGCCGGGCACA
GACCAAAGACCGCGGTCCAGCCCCGCCAGGCGGGCATCTCATGGCAGTGCGGACCCGTGGCTGGCAGCCCCGGG
AGTCCTTTGCAAAGGCACCCCTTGCTCTTAAATCACTTCGCTATGTGGGAAAGGTGGAGATACTTTTATATATTT
GTATGGGACTCTGAGGAGGTGCAACCTGTATATATATTGCATTCTGCTGACTTTGTTATCCCGAGAGATCCATG
CAATGATCTCTTGCTGTCTTCTGTCAAGATTGCACAGTTGTACTTGAATCTGGCATGTGTTGACGAAACTGGT
GCCCCAGCAGATCAAAGGTGGGAAATACGTGACAGTGGGGCTAAAACCAAGCGGCTAGAAGCCCTACAGCTGCC
TTCGGCCAGGAAGTGAGGATGGTGTGGGCCCTCCCCGCCGGCCCCCTGGGTCCCCAGTGTTTCGTGTGTGCGT
TTGTCTCTGCTGCCATCTGCCCCGGCTGTGTGAATTCAAGACAGGGCAGTGCAGCACTAGGCAGGTGTGAGGAG
CCCTGCTGAGGTCACTGTGGGGCACGGTTGCCACACGGCTGTCAATTTTACCTGGTCACTTGTGACCACCACC
CCCTCCCCCTCACCGCCTCCAGGTGGCCCCGGGAGCTGCAGGTGGGGATGGCTTTGTCTTTGCTCCTGCTCCCCG
TGGGACCTGGGACCTTAAAGCGTTGCAGGTTCTGATTTGGACAGAGGTGTGGGGCCTTCCAGGCCGTTACATAC
CTCTGCCAATTCTCTAACTCTCTGAGACTGCGAGGATCTCCAGGCAGGGTTCTCCCCTCTGGAGTCTGACCAAT
TACTTCATTTTGCTTCAAATGGCCAATTGTGTCAGAGGGACAAAGCCACAGCCACACTCTTCAACGGTTACCAAAC
TGTTTTTGGAATTACACCAAGGTGCGGGCCACTGCAGGCAGCTGGCACAGCGTGGCCCCGAGGGGCTGTGGAAC
GGGTCCCGGAACGTGTGACATGTTTGATTTTAGCGTTTCCTTTGTTCTTCAAATCAGGTGCCCCAAATAAGTGAT
CAGCACAGCTGCTTCAAATAGGAGAAACCATAAAATAGGATGAAAATCAAGTAAAATGCAAAGATGTCCACACT
GTTTTAACTTGACCCTGATGAAAATGTGAGCACTGTTAGCAGATGCCTATGGGAGAGGAAAAGCGTATCTGAAA
ATGGTCCAGGACAGGAGGATGAAATGAGATCCCAGAGTCCTCACACCTGAATGAATTATACATGTGCCCTACCAG
GTGAGTGGTCTTTTGAAGATAAAAACTCTAGTCCCTTTAAACGTTTGCCCTGGCGTTTCTAAGTACGAAAAG
GTTTTTAAGTCTTCGAACAGTCTCCTTTTCATGACTTTAACAGGATTCTGCCCCCTGAGGTGTAATTTTTTTGTTT

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FIGURE 53D

TATTTTTTTCCACGTACTCCACAGCCAACATCACGAGGTGTAATTTTTTAATTTGATCAGAACTGTTACCAAAAAA
CAACTGTCAGTTTTATTGAGATGGGAAAAATGTAAACCTATTTTTATTACTTAAGACTTTATGGGAGAGATTAGA
CACTGGAGGTTTTTAACAGAACGTGTATTTATTAATGTTCAAAACACTGGAATTACAAATGAGAAGAGTCTACAA
TAAATTAAGATTTTTGAATTTGTACTTCTGCGGTGCTGGTTTTTCTCCACAAACACCCCCGCCCCCTCCCCATGCC
CAGGGTGGCCGTGGAAGGGACGGTTTACGGACGTGCAGCTGAGCTGTCCGTGTCCCATGCTCCCTCAGCCAGTGG
AACGTGCCGGAACTTTTTGTCCATTCCCTAGTAGGCCTGCCACAGCCTAGATGGGCAGTTTTTGTCTTTCACCAA
ATTTGAGGACTTTTTTTTTTTTGCATTATTTCTTCAGTTTTCTTTTCTTGCACTGATCTTCTCCTCTCCTTCTG
TGACTCCAGTGACTCAGACGTTAGACCTCTTGATGTTTTCCCACTGGTCCCTGAGGCTCTGTTC

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FIGURE 54

MAPPPPPVLPVLLLLAAAAALPAMGLRAAAWEPRVPGGTRAFALRPGCTYAVGAACTPRAPRELLDVGRDGRLAG
RRRVSGAGRPLPLQVRLVARSAPTALSRRRLRARTHLPGCGARARLCGTGARLCGALCFVPVGGCAAQHSALAAP
TTLPACRCPPRRPRPCGRPICLPPEGGSVRLRLLCALRAAGAVRVGLALEAATAGTPSASPSPSPPLPPNLPEA
RAGPARRARRGTSGRGSCLKFMPMPNYQVALFENEPAGTLILQLHAHYTIEGEEERVSYMEGLFDESRGYFRIDS
ATGAVSTDSVLDRETKETHVLRVKAVDYSTPPRSATTYITVLVKDINDHSPVFEQSEYRERVRENLEVGYEVLTI
RASDRDSPINANLRYRVLGGAWDVFQLNESSGVVSTRAVLDRREEAAEYQLLVEANDQGRNPGPLSATATVYIEVE
DENDNYPQFSEQNYVVQVPEDVGLNTAVLRVQATDRDQGQNAATHYSILSGNVAGQFYLHSLSGILDVINPLDFE
DVQKYSLSIKAQDGGRPPLINSSGVVSVQVLDVNDNEPIFVSSPFQATVLENVPLGYPVVIQAVDADSGENARL
HYRLVDTASTFLGGGSAGPKNPAPTDFPFQIHNSSGWITVCAELDREEVEHYSFGVEAVDHGSPPMSSSTSVSI
TVLDVNDNDPVFTQPTYELRLNEDAAGSSVLTQLQARDRDANSVITYQLTGGNTRNRFALSSQGGGLITLALPL
DYKQEQQYVLAVTASDGTRSHTAHVLINVTDANTHRPVFQSSHYTVSVSEDRPVGTSIATLSANDEDGTENARIT
YVIQDPVPQFRIDPDGMTMYTMMELDYENQVAYTLTIMAQDNGIPQKSDTTTLEILILDANDNAPQFLWDFYQGS
IFEDAPPSTSIQVSATDRDSGPNGRLLYTFQGGDDGDGDFYIEPTSGVIRTQRRLDRENVAVYNLWALAVDRGS
PTPLSASVEIQVTILDINDNAPMFEKDELELFVEENNPVGSVVAKIRANDPDEGPNAQIMYQIVEGDMRHFFQLD
LLNGDLRAMVELDFEVRREYVLVVQATSAPLVSRATVHILLVDQNDNPPVLPDFQILFNMYVTNKSNSFPTGVIG
CIPAHDPDVSDSLNYTFVQGNELRLLLLDPATGELQLSRDLNDRPLEALMEVSVSDGIHSVTAFCTLRVTIITD
DMLTNSITVRLENMSQEKFLSPLALFVEGVA AVLSTTKDDVFVFNVDNDTDVSSNINVTFSALLPGGVRGQFF
PSEDLQEQIYLNRTLTTTISTQRVLPFDDNICLREPCENYMKCVSVLRFDSSAPFLSSTTVLFRPIHPINGLRRCR
CPPGFTGDYCETEIDLCYSDPCGANGRCRSREGGYTCECFEDFTGEHCEVDARSGRANGVCKNGGTCVNLLIGG
FHCVCPPGEYERPYCEVTTRSFPFQSFVTFRGLRQRFHTISLTFATQERNGLLLYNGRFNEKHDFIALEIVDEQ
VQLTFSAGETTTTVAPKVP SGVSDGRWHSVQVQYYNKPNIGHLGLPHGPSGEKMAVVTVDCCDTTMAVRFGKDIG
NYSCAAQGTQTGSKKSLDLTGPLLLGGVNP LPEDFPVHNRFVGC MRNLSVDGKNVDMAGFIANNGTREGCAARR
NFCDGRRQCNGGTCVNRWNMYLCECPLRFGGKNCEQAMPHPQLFSGESVVSWSDLNIIISVPWYLGLMFRTRKED
SVLMEATSGGPTSFRLQILNNYLQFEVSHGPSDVESVMLSGLRVTDGEWHHLIELKNVKEDSEMKNLVTMTLDY
GMDQNKADIGGMLPGLTVRSVVVGASEDKVSVRRGFRGCMQGV RMGGTPTNVATLNMNNAKVRVKDGCDDVDDP
CTSSPCPPNSRCHDAWEDYSCVCDKGYLGINCVDACHLNP CENMGACVRSPGSPQGYVCECGPSHYGPYCENKLD
LPCPRGWWGNFVCGPCHCAVSKGFDPCNKNTNGQCQCKENYYKLLAQDTC

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FIGURE 55

GGCACGAGGGCCCCGGCGGCAGGTCCCAGCCCCGGGGCTAGAGACCGAGGGCCGGGGTCCGGGCCCCGGCGGGGGAC
CCAGGCGGTTGAGGCTGGTCAGGAGTCAGCCAGCCTGAAAGAGCAGGATGGATCTTGATGTGGTTAACATGTTTG
TGATTGCGGGCGGCACGCTGGCCATCCCAATCCTGGCATTGTGGCTTCATTTCTTCTGTGGCCTTCAGCACTGA
TAAGAATCTATTATTGGTACTGGCGGAGGACATTGGGCATGCAAGTCCGCTATGTTACCATGAAGACTATCAGT
TCTGTTATTCCCTCCGGGGCAGGCCTGGGCACAAACCCTCCATCCTCATGCTCCACGGATTCTCTGCCCCACAAGG
ATATGTGGCTCAGTGTGGTCAAGTTCCTTCCAAAGAACCTGCACTTGGTCTGCGTGGACATGCCAGGACATGAGG
GCACCAACCCGCTCCTCCCTGGATGACCTGTCCATAGATGGGCAAGTTAAGAGGATACACCAGTTTGTAGAATGCC
TGAAGCTGAACAAAAAACCTTTCCACCTGGTAGGCACCTCCATGGGTGGCCAGGTGGCTGGGGTGTATGCTGCTT
ACTACCCATCGGATGTCTCCAGCCTGTGTCTCGTGTGTCTGCTGGCCTGCAGTACTCAACTGACAATCAATTTG
TACAACGGCTCAAAGAACTGCAGGGCTCTGCCGCCGTGGAGAAGATTCCCTTGATCCCGTCTACCCAGAAGAGA
TGAGTGAAATGCTTCAGCTCTGCTCCTATGTCCGCTTCAAGGTGCCCCAGCAGATCCTGCAAGGCCTTGTGATG
TCCGCATCCCTCATAACAACCTTCTACCGAAAGTTGTTTTTGGAAATCGTCAGTGAGAAGTCCAGATACTCTCTCC
ATCAGAACATGGACAAGATCAAGGTTCCGACGCAGATCATCTGGGGGAAACAAGACCAGGTGCTGGATGTGTCTG
GGGCAGACATGTTGGCCAAGTCAATTGCCAACTGCCAGGTGGAGCTTCTGGAAAACCTGTGGGCACTCAGTAGTGA
TGGAAAGACCCAGGAAGACAGCCAAGCTCATAATCGACTTTTTTAGCTTCTGTGCACAACACAGACAACAACAAGA
AGCTGGACTTGAGGCCCCGACTGCAGCCTGCATTCTGCACACAGCATCTGCTCCCATCCCCAAGTCTGACGCAGC
CACCCTCTCAGGGATCCTGCCCCAAATGCGGTGCGAGCGCCAGTGACCCTGAGGAAGCCCGTCCCTTATCCCTG
GTATCCACGGTTCCCCAGAGCTTTGGGGACCACGCGAAAAACCTCCAAGATATTTTTACAAAATAGAACTCATA
TGGAACAAAAATAAGAAACCCAGCCATGAAATCTACCATGAAGTCTTCAAGTTCATGTCACTGAGAAGCTTGTGC
AAAGCAGCCACCTTGACCATAATTAAATCAAGGACATTTTTCTTTGAGACATTCCTTATAGTTGGAGACTCAAGA
TATTTTTGTTGCATCAGGTGTATTCCCTTGATGGGCAGTGGCTTTTATAGGAGCATTAGTCCTCATTGCTGAA
CCCTGTTGTTTAGGTCTAATTTAAGTTTTACATAGAGACCCATGTATGACTGCAGCCCATTGGCTGCAAGACCAG
GGAGGAAAGTGGCAAGCTGTAGAAAATGTTTACACGCATGGAGGGGCATTGCTCTAGCCCTCAGAGCGTCCGGAG
CAGCAGGGTACATGGGTGGGAGGTTCAATTCAGCACCCACCAGTCAGGTATGTTCTGAGTGAACCCACAGCAGTCG
CAGAATGAGCACCTGGCAGGGTGGGTTTCTAGGAATAATTTATTATTTTTAAAAATAGGCCTAATAAAGCAATA
ATGTTCTAGACATCTGTCTAAGTAATCAGACTCAGGTTCCACACACAAGCAACAACCTCGTGGGCCTCTTTTCTAT
TTCAATGTGCTACTAAGAACCCTTGATGTAACTACTAGTTAGTTAATGAATTCTGTGAATTCTGTGAAGAGTA
ATGTGATTGAAAATAAGTCTAAACAGCTGTAAAAGTGACCACAATGACATGAAATAAATTTAATAAGTCTAGATC
AGCAAAAAAAAAAAAAAAAAAAAA

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FIGURE 56

MDLDVVNMFVIAGGTLAIPILAFVASFLLWPSALIRIYYWYWRRTLGMQVRYVHHEDYQFCYSFRGRPGHKPSIL
MLHGFSAHKDMWLSVVKFLPKNLHLVCVDMPGHEGTTRSSLDLSDGQVKRIHQFVECLKLNKKPFHLVGTSMG
GQVAGVYAAYYPSDVSSLCLVCPAGLQYSTDNQFVQRLKELQGSAAVEKIPLIPSTPEEMSEMLQLCSYVRFKVP
QQILQGLVDVRIPHNNFYRKLFLEIVSEKSRYSLHQNMDDKIKVPTQIIWKGQDQVLDVSGADMLAKSIANCQVEL
LENCGHSVVMERPRKTAKLIIDFLASVHNTDNNKKLD

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FIGURE 57A

GGAACACAAAACACTGCGGCCCTTGTCTGCAAACAGTGGTATCGACTTATCAAAGGTGTAGCCCATCAGTGTTATCA
TGGTTTCATGAAGGCTGTCCAGGAAGGAAACATTTCAGTGGGAGAGCCGTACCTATCCTTATCCTGGAACCCCAAT
CACTCAGCGCTTCTCGCACAGTGCATGCTATTATGATGCTAATCAGTCTATGTATGTGTTTGGAGGCTGTACCCA
GAGCAGCTGCAATGCTGCTTTCAATGACCTCTGGAGACTTGACCTAAACAGCAAAGAGTGGATCCGACCTTTGGC
TTCAGGGTCTATCCTTCCCCCAAAGCTGGAGCAACTCTGGTCGTGTACAAGGACTTGCTAGTGCTGTTTGGTGG
CTGGACGCGGCCAAGCCCTTATCCCCTACACCAGCCAGAGAGATTCTTTGATGAAATACACACTTACTCACCCCTC
TAAAAATTGGTGGAACGCATTGTGACAACCCATGGGCCACCTCCCATGGCTGGCCACTCCTCCTGTGTGATAGA
TGATAAAATGATTGTCTTTGGTGGCTCTTTAGGATCCCGGCAAATGAGCAATGATGTCTGGGTCTTTGACCTTGA
GCAGTGGGCGTGGTCCAAGCCGAACATCTCTGGCCCCAGTCTCATCCTCGAGGTGGCCAATCTCAGATTGTCA
AGATGATGCAACTATCTTAATCCTCGGAGGGTGTGGCGGTCCCAATGCTCTATTCAAGGATGCTTGGTTGTTGCA
CATGCATTCTGGTCTTTGGGCTGGCAGCCACTCAAGGTAGAAAATGAAGAGCATGGGGCCCCAGAAGTGTGGTG
CCATCCAGCTTGCCGGGTGGGACAGTGTGTGGTGGTCTTCAGCCAGGCTCCTAGTGGGAGAGCCCCACTCAGCCC
CAGTTTGAAGTCTCGCCCATCACCTATCAGTGCCACTCCTCCAGCTCTCGTTCCTGAAACCCGAGAGTACCGCTC
TCAGTCTCCAGTAAGAAGCATGGATGAAGCTCCTTGTGTTAACGGCCGCTGGGGAACACTGAGACCCAGGGCTCA
AAGGCAGACTCCTTCAGGTTCCCGGGAAGGGAGCCTTTCCCCAGCCAGAGGAGACGGCTCTCCTATCCTCAATGG
TGGGAGTTTGTCTCCAGGAACGGCAGCTGTGGGTGGCTCTTCTTTGGACAGTCTGTACAGGCCATATCTCCAAG
TACTCCATCTGCTCCTGAAGGATACGACCTGAAAATAGGACTTTCTTTGGCCCCCGACGAGGATCACTACCAGA
TCAGAAAGATCTGAGATTAGGATCCATAGATCTGAATTGGGATCTGAAACCCGCTTCCAGTAGTAATCCCATGGA
TGGCATGGACAATAGGACAGTTGGGGGAAGTATGAGACACCCCTCCTGAACAGACAAATGGTGTGCATACCCCCACC
TCACGTGGCCAGTGCCCTTGCAGGGGCCGTCTCCCCAGGTGCCCTGCGTCGGAGTCTGGAAGCCATCAAAGCGAT
GTCCTCCAAAGGCCCTCGGCCTCTGCAGCACTAAGTCTCCTCTTGGGTCTTCTCCAGGCTCTCCTGGGAGCCA
GAGTTTGAGCAGTGGAGAAACAGTGCCCATCCCTCGCCCAGGGCTGCCAAGGAGATGGACATTCTTACCTCC
CATTGCTCGCCGCTGGGCCACCACCCTCCACAGTCCCTAAATGTTGGCAAACCCCTATACCAGAGTATGAACTG
CAAGCCCATGCAGATGTACGTGCTGGACATTAAAGACACCAAGGAGAAGGGGCGGGTCAAATGGAAAGTATTTAA
TAGCAGTTCTGTGGTTGGACCTCCTGAAACCAGCCTGCATACCGTGGTACAAGGCAGGGGTGAAGTCAATCATAT
TGGAGGACTCATGGACAAGAAACAGAATGTGAAGTACTATCCAAAAACAAACGCCTTGTACTTTGTACGAGCAAA
GAGATTAATGTGTTCTAAACCCCTTTCTTTTCTGTGGCTTTTAATTTGGAATTTTCCAGTGTGTAAGCATTGGA
CTGAGAATTGGGAAAACAAAATTACTCCCAGAAGCCAAAACCTTTTAATTTCCCAACCGAAGTCACTCCAGGCTGG
GATCAAATCTCCATTAAAGAAAAAAATTATATATAAATATATATATATATATATATAGCCAACTCTGTTGACAA
AAAAAGGGAGAGATTTCCATCCTGGTTCAGATAAAGTTGTTGCTGTGTTTTAACAGGGGCTGGGCTGCCTTTTTC
TACCTTGCTGGTAACTAGACCAAGAAGTTAGAGAATAGACTAACATCAGTAACTTCCCAAAAGAACTGAAGAGC
CCCCTGTAATCTTTATGTGGCCTTCTTGGAGTTAAAAAATGAAAGGGCATATGTAAGTTGCAAAGGTGGAGGGT
TTTAGACTCTCATGCTTCAGGTGCTGTGCGGGTAAAGTAAGTGTGTTTTCCCTTCTCTTAAACCACAGAGGAC
CTGTGACAGCTCTGCAGAAATGCCAGTGCCTGGCCCCCTCTTGCCTTTTATGGCTGAGGAAAGTTACCCAACAAA
GGATTTTATTCCACATTTGTGTGCCGGGTCAATTGTGAAATAATGTTTATGCAGCCAACATCTGACCGCCTAGTAG
TGTCCATTGGTCTTTGGAGTGCTTCTTGTGTGTCTCAGAAAAATTTTGTGTCTGATTGTGGAATTTCTGACAA
TCAATCATATTTGGTGGCAAGTTGCCAAAAAACATATTTATTCTCCTCTTTCTTCCCTTAGAACATGGTACTTGG
AAACTGCCTTTTCCATTCACTTACAGGCTGCTTTTTTCTTCTACCTTTTTTCTTTTCTTTTTTTTTTTCATATG
TGGTGAAGTCCTAAACCTGTCTGACTTTCTGTTTCTTTTACAAAGCTCAGGTGCCTACAGAAATCAGAAGCTGC
TTAGAAATACCTTGTGGAACCCCTTTCCCTGGTGTCACTAGGGGGCCAGTAGGGAATTCTAAGATGCCAATATTGTG
AGAAATCTTTGAAGCAAGCATCAAAGATACTGTTTTTCCCTATGGGCTTCTTTTTACTTCCAAAGCACATTGA
GCACACTCATCCCATATTTGTAGAATGTGGAAATTGATTCTGGAAGGGAATTCCAATAACAGTTCTTTTTTAGAAA
TGTTTTTTTCTTGTGGTGACATATATTCCTCTTCTTGGCTATTGGCAGGTGATGGAGTTGAGAATCATGTACTT
GACTTCTTGACGCATGGCTGACCTCAGAAACAGCTCCATCCTTTGCACTTGTCTTCTTCATGTGTACCCAAATA
GGGCTTGGGTTTTTACTTTCACTTCATTTCTGAGATTAAGGTGTAACCAAGTAGAGCATTTCTTTGCTTGATACA
GAAAGTTACTAGTCTCAACCATGGCCTGGGCATAGGAGATGTCAAATAAGTTTATTTCAAATGGCACCATTAA
ATAGGGATTTTTGGTGATTTCTCATCAGTGGAAGAGGATTTTTGTTTTGCCTTTGTTTTGTTTTGAAATTTAA
TCCTAATTTCAAACATCACCTTGCCACCCTGACACTCCTCTTTTTATTATTAGCGTTTCTCAGGCACAAAGCCT

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FIGURE 57B

GCTGCAGCTGGCCCTGGGTCCTGGCTTTTCAGCCAGCATCTGGCAGCCTAAGTGTACTGATAAGTGTGTTTTCTCC
TGTTACATCATGCTGAATCCTTTCCCTTAGCCATTAGCTTTTATGATGTGGTCTTCGTAGGAAAGCCACCCTGGT
GCCAAGCCTAGCTTGTGGGGAGGGGTATGTGTTCCAGAACTGCTCTTTGTGTTCCCTTCAATGAGGAAACAACA
TGTGTCTACTTATGTGGCATCCAAGTGTGGAGCTCCACACTTCCCTTTCGCGACTCAGGCTCTGGTGTCTGTG
CCAATCCTTGCTTGGCAAAGACTGTTTCGATCATGTGGGGTCCTTATTTACAAGGGAAAGCTGGGCCAGAAGGCTA
GCAATTCAGGTGTTACCGCTATTGCTGTACCTTGTGTTAGGACATTGTGTTTGTGCATGGACTGTGCCTCCAAAC
TCAGTAGTTTCTATCTAAATATAAAGTATATTAGAAACCTGAAAGTACAGAATCTCAACCTTACAGTCTTTCCCT
TAGTCCTGTGGCCTTCCTAAGCCAGCTGTTAACGTGTTGATTTCCTTCCACTTCCCCCAAGTAGGCAGGCAACAGA
TATGTTGATTGTCTTAGAAAAGTAATCTGGTTCCTCTGAACTCCATTGAATTCCAGTTTGACGCATACTGCCTGGA
ACCAGACTGTTTGTCTTACAGCTTTTTAAGAAAAATCTGCCTTGTCTGCCCCCATTATGGTTGGTCTTGGTAGCTC
CTGGGCACTGTGGGCGTGTACCATGGGAAAGTGATTCAACACAGTGAAAGGTGATTGTCTCCTCAGGCCTCCTGAA
GCCACCTGTGCGGTGGGACTTCACGTGTCTCGGCCAAGGCGAGCATTTCCACAATGCCGTGGATGCTGCAGTCAG
GCCAGATTGAACCATGACCCCATTTTTTCACATGATAACCAATTTTGTCTTAAAATTCAGTGAAGAAATGAGACTA
AATTTTTTTTTAACCCCTCAGGAGCACCTGAAGCAAATATTTATCCGTATTTATTGAAAATTCATTTTGTCTTACT
TGAAGCTTTTAAACCCCTTCCATTCCCTGCAAGTGTGCCTTTTGAGAGCTCCCATGGCCTAGTGACTTCACTGGTCAC
CTTGTCCATCTTACTTAAAGATTTTAGTCTCTCCCTACCCTCTTGGACAGAGCTTCCCTGTTCTCTTATTTACAG
GTTATACAGCAGAGCGGGTTTTGTGTTTTTCATTCCCTATTTCCACCCTTCATTTGGTTGGTGGACTCCACAACCTC
ACCCTACCCTACACTTTGGGAGCACAAATTTGGTGTGTAACAAGCTTAAATTTCAATTTAGGGCATACTGGGCT
TACTCTCCTCCCAGCTGTCTGTGGATTGATTTGATTTTAAATGTTTCGAGTTTTACAGCAACAGCTGAAAACCATGA
ACTATTCTAGGAAGTGTGTTGGAAGTCTTTAAAATAAAGAAAAGAGGAGGAGGAGGAAGAAAGAAAACCAAC
TTAAGAAGCCTTGACTTTGGAGGACAGAAAGCCACCAGCCAATGGAGAACAAGAGATGTTTCCCTTTCCCTTTCT
TTCACCTTGTCAATCTGGGTTTTCTTCTGCTTCACTCTTTCCCTTCCCCCTTAAAAGTGGTATTCCCTGGTTGGTCT
GTCTGTCTGTCTTGTCTTGTGGTGATCCTGGCATGGTGATATGCTCCACTTTCATTATCCATGGTCTCTTAC
CAGCGCACAAAGTCAGTGGGAGGATCTAACCACGCCTGGTGGTGAGGAAGCTGAATTTCCAGGCCTGCGTCCCAT
GTAGCCTCTCCATGAAGTGCAGAAGGCATGTTCTGCATGGTTACCAGTAAGTGGCTCCCTCTCACCGTGTTCATT
GTCAAATGAGAGCAAACCTTTAGGTGTTGGCTCCATTGTACACTCTACTTGCTCTGCTCCCTCCCTCCAACCAGG
GTTTATGTGTCAGTGCACACCCCATGTGCCCTGGCGAAGCTGGTGTGTGAGTGATGTTTCCCATACAACCTCAGGGA
TGCCAGGTGGCTTACCCTGAGATAGTCATTTTGGGCACATAACAGTGTAGGAATGAAACATGGATTTTATTGATA
TTTAAATCTGTCAATTTTCAATTTTTGTAAATGTTTTCCCTGATGACTTTTTTAGCAATTTAACAATAAAATGGA
CAATTGTCTTAAC

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FIGURE 58

EHKTAALVCKQWYRLIKGVAHQCYHGFMKAVQEGNIQWESRTYPYPGTPITQRFSHSACYYDANQSMYVFGGCTQ
SSCNAAFNDLWRLDLNSKEWIRPLASGSYPSPKAGATLVVYKDLLVLFGGWTRPSPYPLHQPERFFDEIHTYSPS
KNWWNCIVTTHGPPPMAGHSSCVIDDKMIVFGGSLGSRQMSNDVWVLDLEQWAWSKPNI SGPSPHPRGGQSQIVI
DDATILILGGCGGPNALFKDAWLLMHSGPWAWQPLKVENEEHGAPELWCHPACRVGQCVVVSQAPSGRAPLSP
SLNSRPSPI SATPPALVPETREYRSQSPVRSMDEAPCVNGRWGTLRPRAQRQTPSGSREGSLSPARGDGSPILNG
GSLSPGTAAVGGSSLDSPVQAI SPSTPSAPEGYDLKIGLSLAPRRGSLPDQKDLRLGSIDLNWDLKPASSNPMD
GMDNRTVGGSMRHPPEQTNGVHTPPHVASALAGAVSPGALRRSLEAIKAMSSKGPSASAALSPPLGSSPGSPGSQ
SLSSGETVPIPRPGPAQGDGHS LPP IARRLGHHPPQSLNVGKPLYQSMNCKPMQMYVLDIKDTKEKGRVKWKVFN
SSSVVGPPETSLHTVVQGRGELIIFGGLMDKKQNVKYYPKTNALYFVRAKR

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FIGURE 59

GCTCTGGCGGGCTCCCGCGGCTCCGGCTGGCGGCTTCGGGGCCCTGCACCTGTGACTCTCGGCCGCGCTCGCCCTCG
GCCCCGCGCGCGCCGCGAGCCCCATGGCCCCGTCCAGGCTGCAGCTCGGCCTCCGCGCCGCCTACTCCGGCATCAG
CTCCGTGGCGGGCTTCTCCATCTTCCTCGTCTGGACGGTGGTCTACCGACAGCCGGGGACCGCGGCCATGGGAGG
GCTCGCAGGGGTGCTGGCACTGTGGGTCTGGTGACGCACGTGATGTACATGCAAGATTATTGGAGGACCTGGCT
CAAGGGGCTGCGCGGCTTCTTCTTCGTGGGGGTCTCTTCTCGGCCGTCTCCATCGCTGCCTTCTGCACCTTCCT
CGTGCTGGCCATCACCCGGCATCAGAGCCTCACAGACCCACCAGCTACTACCTCTCCAGCGTCTGGAGCTTCAT
TTCCTTCAAGTGGGCTTCCTGCTCAGCCTCT**ATG**CCACCGCTACCGGGCTGACTTTGCTGACATCAGCATCCT
CAGCGATTTCTGACCCAGGGGGTGAGGTCTCTGCACCCTGGGGGGGCTTAGGACCTGGACTCAGCCTCTGAGAT
GTTGGGAGAGGCTACTCCACCCCTGGTGACCCAGAACTGTGGCAGAAAATACACAGCAGGACGAGTGTGGTC
TCCCAGGAAGCTGTCTGCCGTCCCTTTTCGAGGAAACCTGAGTGTGGTAGAGAGGGGATCCTGCCATGTTGCT
CCTCATCAGCCTGGCCAGAGGGCAGCTTTAGACCTTTTCAAATGAATCTGTTTTCTTTCTTTTCTTTTCTTTTCT
TTTTTTTTTTTTTTTTTGAGATGGAGTCTTACTCTGTACCCAGGCTGGAGTGCAGTAGTGCATCTCAGCTCACT
GCAACCTCCGCTCCAGGTTCAAGCAATTCTCCTGCCTTGGCCTCTCAAGTAGCTGGGATTACAGGCATCTGCC
ACCATGCCCCGCAAAATTTTTGTGTTTTTAGTAGAGACAGGGTTTTGCCATGTTGGCCAGGCTGGTCTCGAACTCC
TGATCTCAGGTGATTCACCCGCTCAGCCTTCCAAAGTGCTGGGATTATAGGTGTGAGCCACCGTGCCCGGCTG
GATCTGTTTTCTTAGCACGCAGTGAGGAATCTTTGTACTTAAGGCCAGGGCAACAAAGTCAAGAGGTCAAGGTG**T**
AGGGCCATGAGGCCTGGACCTATGCTGCAGGCAAGGGTTTCCATCCCCGCTGCCCTAGGCACTCTCTTCCCAAGG
CCAGGTTGGGCACCTGGGGAGGTCAGTTCAAGAAATATCTAGCAGAGACCTCTTAAACCCCATCCCAGCACCCCA
TCCTGTTGTTCCAGAGCTGGTCTCCCATGAGTGTGCTAGAGCCAGATAGCCGTGGCCCCCACCATCTCACTC
ACACACACAGGCATCCATACACCCAGAAAGACTTCCCAAATGAGGCCAGACTCAGGGTCACGGGGAATGTGCTTC
TGCCCCGTGAAGGGCTTTGGGGAAGGGGGCAACATAGTAGAGGCTGGAAAGAGCCCCCAAACCTGTGCCCATGCC
CCTCCAGCCCTGCGTTTCCATTCTGCCTTCTCAGAGTGCCCTTGCTGCACCCAGACCACCGGCCAGGAGAGACCT
TCTCTCCCACTCCAGCCCTCTCACTGCCCTTCAACTAGAGCTTTCACCTTTTTACATTTCCCTTCTGAAGGACA
CAAATCTGCTTTCTGCCATACACTGGCCCAAGGGCTCACCTAACTTGGGAGGGAAGGGGCTGTTGGTACAAGG
ATGATTTTCTGTTAGGCTGCCATTTTGACGGTCTCCCCCTCCCCATCTGATGTGTCCTGCCCTCAGCTCTTTG
CCTTATCTGTGTCAGTGTCACTTTAGCAAAAATACAGCGGCCATTTGTATCAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 60

MPTATGLTLLTSASSAISDPGGEVSAPWGGLRTWTQPLRCWERLLPPPGDPRTVAENTQQDECGLPGSCPAPRLS
RKPECGREGILPCCSSSAWPEGFRPFQMNLFSLFSLFFFLFFFLRWSLTLSRLECSAISAHCNLRPLPGSSNS
PALASQVAGITGICHARQIFVFLVETGFCHVGQAGLELLISGDSFASAFQSAGIIGVSHRARP GSVFLARSEES
LYLRPGQQSQEVKV

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FIGURE 61

ATGGGTGTGCTGGATAGCCGGTTGCACCTGTTTCTTGGGTCTTCTCTCCTGTTCCCACTGTTCCACTTCAGGAGA
GCCAAGCATCTCACCCATGCTCTCATATTAGTCTAGGCATCCTACCCAAGTATCCTAATTATAAACTAGCCACC
AGCTCAGGCTCTGTATCCCAGTCACCACCCCCATTAGGCCCCCAACTATCCAGTGCCAGAGGCCCTCAGGTGCA
GAGGGCCAGTTTCAGCCAAACCAGGACAGACCCAGCCACCCTTGTTTCCAGCCCAGCCTACAAGCCTCCTGAAACC
CACCAGTCTGATGGTAGCCTCCCCCTCCCTGTTTCTCCAGGAAGAAAGAGAAATCGCCTCCCTCCAAAACCAAGCC
CAACCAGAAACCTGTCCCCACCCCTCATCAGCTGCTCCAGATCCGAATGGGATTTGCAGAAGTCCTGAGCACT
GGTGGTTGGTGGGCAGCAACAGGCCCTTTGCGCGGCAGCTGGACGGATGGGGTGGGGGCGAGGTCTGGGCCAGGG
CCTGAGGGTACGGGCACTAAGGCCGAGGCGTCGCCTCCCGGCGCCTCTCCACGGCCACGGCCGAGCGGGCTCCA
CGGCTCCAGGAGTTCGCCGCGCTAGCTGCCTCCCCCTGCGTCCGCGTCTTGAGCTCTGAGCTCTTCACCCTGACC
TATGGTGCCCTGGTCACCCAGCTATGTAAGGACTATGAAAATGATGAAGATGTGAATAAACAGCTGGACAAAATG
GGCTTTAACATTGGAGTCCGGCTGATTGAAGATTTCTTGGCTCGGTCAAATGTTGGGAGGTGCCATGACTTTTCGG
GAAACTGCGGATGTCATTGCCAAGGTGGCGTTCAAGATGTACTTGGGCATCACTCCAAGCATTACTAATTGGAGC
CCAGCTGGTGATGAATTTCTCCCTCATTTTGGAAAATAACCCCTTGGTGGACTTTGTGGAACCTTCCTGATAACCAC
TCATCCCTTATTTTATTCCAATCTCTTGTGTGGGGTGTGCGGGGAGCTTTGGAGATGGTCCAGATGGCTGTGGAG
GCCAAGTTTGTCCAGGACACCCTGAAAGGAGACGCCGCGAGGGGCGGCCGCGAGAGCGACGCGGAACCCCGCCGG
CGCGGACCCCGGACCCCAACGCCGCCCGCCAGCCGCGGACGCCCTGCCCGGAGCCCTCGCCGCCCGGGCCGCC
CTCGAGGGCCCGGAGCGGCGCCCGCGGCCGCGCCCGCAGGCCCTGCCTCTGCTGGAACCTTCCAGGCCCTCC
GACCTGAAAGCCCAGCCCTCCTGCTGCCGCTGCTGCCGCCACCACGCAGGGTAGCCGAGAGGCCAGGAATCT
TGGCAGGCGTGCGGAGGCAGCGGGTGGCGGGTGGCGCTCCGGAAGAGGCTGCAAATGCGAACCAGAAGCACGTCC
ACGGACGCCATGCTGGGACTCTGACACCCCTGTCTTCGCTGCTGCTGCTGCTACTGGTGCTGGTGCTGGGGTGT
GGGCCGCGGGCTCCTCTGGTGGCGGGGCCGGTGGGGCGCGGGCTATGCCCCAGTGAAGTACATCCAGCCCATG
CAGAAAGGACCTGTGGGACCGCCCTTCCGTGAGGGCAAAGGCCAGTACCTGGAATGCCTCTACCGCTGCTGCCG
ATGGACCTGAAGGGAGAGCCCGGCCCCCTGGGAAGCCCGGGCTCGGGGTCCCCCTGGCCCCCTGGCTTCCCA
GGAAAACAGGCATGGGAAAGCCAGGACTCCATGGGCAGCCTGGCCCTGCTGGGCCCTTGCTTCTCCCGATG
GGCAAGGCTGGTCCCCAGGGCTCCCTGGCAAGGTGCGGGCCACCAGGGCAGCCGGGGCTTCGGGGGAGCCAGGA
ATACGAGGGGACCAGGGCTCCGGGGACCCCAAGGACCCCTGGCCTCCCGGGCCCTCAGGCATTACTATCCCT
GGAAAACAGGTGCCCAAGGGGTGCCAGGGCCCCCAGGATTCAGGGGGAACCAGGGCCCCAGGGGAGCCTGGG
CCCCAGGTGATCGAGGCCTCAAGGGGGATAATGGAGTGGGCCAGCCGGGCTGCCTGGGGCCCCAGGGCAGGGG
GGTGCCCCCGCCCCCCCCGGCCTCCCTGGTCCAGCTGGCTTAGGCAAACCTGGTTTGGATGGGCTTCTGGGGCC
CCAGGAGACAAGGGTGAGTCTGGGCCTCCTGGAGTTCCAGGCCCCAGGGGGGAGCCAGGAGCTGTGGGGCCAAAA
GGACCTCCTGGAGTAGACGGTGTGGGAGTCCAGGGGCAGCAGGGTTGCCAGGACCACAGGGCCCATCAGGGGCC
AAAGGGGAGCCAGGGACCCGGGGCCCCCTGGGCTGATAGGCCCCACTGGCTATGGGATGCCAGGACTGCCAGGC
CCCAAGGGGGACAGGGGCCAGCTGGGGTCCAGGACTCTTGGGGGACAGGGGTGAGCCAGGGGAGGATGGGGAG
CCAGGGGAGCAGGGCCACAGGGTCTTGGGGGTCCCCCTGGACTTCCTGGGTCTGCAGGGCTTCTGGCAGACGT
GGGCCCCCTGGGCCTAAGGGTGAGGCAGGGCCTGGAGGACCCCCAGGAGTGCCTGGCATTCGAGGTGACCAGGGG
CCTAGTGGCTGGCTGGGAAACCAGGGGTCCAGGTGAGAGGGGACTTCTGGGGCCCATGGACCCCTGGACCA
ACTGGGGCCCAAGGGTGAGCCGGGTTTACGGGTGCGCCCTGGAGGACCAGGGGTGGCAGGAGCCCTGGGGCAGAAA
GGTGACTTGGGGCTCCCTGGGCAGCCTGGCCTGAGGGGTCCCTCAGGAATCCAGGACTCCAGGGTCCAGCTGGC
CCTATTGGGGCCCCAAGGCCTGCCGGGCCTGAAGGGGGAACCAGGCCTGCCAGGGCCCCCTGGAGAGGGGAGAGCA
GGGGAACCTGGCACGGCTGGGCCCACGGGGCCCCCAGGGGTCCCTGGCTCCCCTGGAATCACGGGCCCTCCGGGG
CCTCCCGGGCCCCCGGGACCCCTGGTGCCCTGGGGCCTTCGATGAGACTGGCATCGCAGGCTTGACCTGCC
AACGGCGGTGTGGAGGGTGCCGTGCTGGGCAAGGGGGGCAAGCCACAGTTTGGGCTGGGCGAGCTGTCTGCCCAT
GCCACACCGCCTTCACTGCGGTGCTCACCTCGCCCTTCCCCGCCTCGGGCATGCCCGTGAATTTGACCGGACT
CTCTACAATGGCCACAGCGCTACAACCCAGCCACTGGCATCTTCACTGCCCTGTGGGCGGCGTCTACTACTTT
GCTTACCATGTGCACGTCAAGGGCACCAACGTGTGGGTGGCCCTGTACAAGAACAACGTGCCGGCCACCTATACC
TACGATGAGTACAAGAAGGGCTACCTGGACCAGGCATCTGGTGGGGCCGTGCTCCAGCTGCGGCCCAACGACCAG
GTCTGGGTGCAGATGCCGTGCGACCAGGCCAACGGCCTTACTCCACGGAGTACATCCACTCCTCTTTTCAGGA
TTCTTGCTCTGCCCCACAT**TAA**

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FIGURE 62

MGVLDSRLHLFLGSSLLFPLFHFERRAKHLTHALIFSLGILPKYPNYKLATSSGSVSQSPPPPFRPPTIQCQRPSGA
EGQFSQTRTDPATLVSSPAYKPPETHQSDGSLPSLFSQEEREIASLQNAQAPETCPHPLISCSQIRMGFAEVLST
GGWWAATGPLRGSWTDGVGARSQPGPEGTGTAEASPPGASPTATAERAPRLQEFALAASPCVRVLSSELFTLT
YGALVTQLCKDYENDEDVNKQLDKMGFNIGVRLIEDFLARSNVGRCHDFRETADVIKVAFKMYLGITPSITNWS
PAGDEFSLILENNPLVDFVELPDNHSSLIYSNLLCGVLRGALEMVQMAVEAKFVQDTLKGDAARGGRQSDAEPRR
RGPRTPTPPAQPRTPPLPGALAAARAALEGRRERPAAAPAGPASAGTFPGPSDLKAQPLLLPLLPPLRRVAEEAQES
WQAWGSGWRVALRKRLQMRTRSTSTDAMLGTLTPLSSLLLLLLVLVLGCGPRASSGGGAGGAAGYAPVKYIQPM
QKGPVGPFFREGKGQYLEMPLPLLPMDLKGEPPPGKPGPRGPPGPPGFPKPGMGKPLHGGQPGPAGPPGFSRM
GKAGPPGLPGKVGPPGQPLRGEPGIRGDQGLRGPPGPPGLPGPSGITIPGKPGAQGVPPGPFQGEPPGQGEPPG
PPGDRGLKGDNGVGQPLPGAPGQGGAPGPPGLPGPAGLGKPGLDGLPGAPGDKGESGPPGVPGPRGEPGAVGPK
GPPGVDGVGVPGAAGLPGPQGPSGAKGEPGTRGPPGLIGPTGYGMPGLPGPKGDRGPAGVPGLLGDREGPEGEDGE
PGEQGPQGLGGPPGLPGSAGLPGRRGPPGPKGEAGPGPPGVPGIRGDQGPSGLAGKPGVPGERGLPGAHGPPGPF
TGPKGEPGFTGRPGPGVAGALGQKGDGLPGQPLRGPSGIPGLQGPAGPIGPQGLPGLKGEPPGLPGPPGEGRA
GEPGTAGPTGPPGVPGSPGITGPPGPPGPPGPPGAPGAFDETGIAGLHLPNGGVEGAVLGKGGKPPQFGLGELSAH
ATPAFTAVLTSPFPASGMPVKFDRITLYNGHSGYNPATGIFTCPVGGVYFAYHVHVKGTNVWVALYKNNVPATYT
YDEYKKGyLDQASGGAVLQLRPNDQVWVQMPDQANGLYSTEYIHSSFSGFLLCPT

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FIGURE 63

GTTGCCGCTGCGCACCTGGCTCAGGTGAGCTGCCCCGCCCCCGCCGGCGCGAGCCCCAGGTCTTGGCAGCAGCC
CCTGACCTGTCCAGGTGCCCTGTCCAGCTGACTGCAAGGACAGAGAGGAGTCCCTGCCAGCTCTTGGATCAGTCT
GCTGGCCGAGGAGCCCGGTGGAGCCAGGGGTGACCCTGGAGCCCAGCCTGCCCGAGGAGGCCCGGCTCAGAGC
CATGCCAGGTGTCTGTGATAGGGCCCTGACTTCCTCTCCCCGTCTGAAGACCAGGTGCTGAGGCCTGCCTTGGG
CAGCTCAGTGGCTCTGAACCTGCACGGCTTGGGTAGTCTCTGGGCCCCACTGCTCCCTGCCTTCAGTCCAGTGGCT
GAAAGACGGGCTTCCATTGGGAATTGGGGGCCACTACAGCCTCCACGAGTACTCCTGGGTCAAGGCCAACCTGTC
AGAGGTGCTTGTGTCCAGTGTCTGGGGGTCAACGTGACCAGCACTGAAGTCTATGGGGCCTTCACCTGCTCCAT
CCAGAACATCAGCTTCTCCTCCTTCACTCTTCAGAGAGCTGGCCCTACAAGCCACGTGGCTGCGGTGCTGGCCTC
CCTCCTGGTCTGCTGGCCCTGCTGCTGGCCGCCCTGCTCTATGTCAAGTGCCGTCTCAACGTGCTGCTCTGGTA
CCAGGACGCGTATGGGGAGGTGGAGATAAACGACGGGAAGCTCTACGACGCCTACGTCTCCTACAGCGACTGCCC
CGAGGACCGCAAGTTCGTGAACTTCATCTAAAGCCGCAGCTGGAGCGGCGTCGGGGCTACAAGCTCTTCCTGGA
CGACCGCGACCTCCTGCCGCGCGCTGAGCCCTCCGCCGACCTCTTGGTGAACCTGAGCCGCTGCCGACGCCTCAT
CGTGGTGCTTTTCGGACGCCTTCCTGAGCCGGGCCTGGTGACCCACAGCTTCCGGGAGGGCCTGTGCCGGCTGCT
GGAGCTCACC CGCAGACCCATCTTCATCACCTTCGAGGGCCAGAGGCGCGACCCCGCGCACCCGGCGCTCCGCCT
GCTGCGCCAGCACCGCCACCTGGTGACCTTGCTGCTCTGGAGGCCCGGCTCCGTGACTCCTTCTCCGATTTTTG
GAAAGAAGTGCAGCTGGCGCTGCCGCGGAAGGTGCGGTACAGGCCGGTGAAGGAGACCCCCAGACGCAGCTGCA
GGACGACAAGGACCCCATGCTGATTCTTCGAGGCCGAGTCCCTGAGGGCCGGGCCCTGGACTCAGAGGTGGACCC
GGACCTGAGGGCGACCTGGGTGTCCGGGGGCCTGTTTTTGGAGAGCCATCAGCTCCACCGCACACCAGTGGGGT
CTCGCTGGGAGAGAGCCGGAGCAGCGAAGTGGACGTCTCGGATCTCGGCTCGCGAACTACAGTGCCCGCACAGA
CTTCTACTGCCTGGTGTCCAAGGATGATATG**TAG**CTCCCACCCAGAGTGCAGGATCATAGGGACAGCGGGGGCC
AGGGCAGCGGCGTCTGCTCTGCTCAACAGGACCACAACCCCTGCCAGCAGCCCTGGGACCCTGCCAGCAGCCC
TGGGAAAAGGCTGTGGCCTCAGGGCGCCTCCAGTGCCAGAAAATAAAGTCCTTTTGGATTCTGAAAAAAAAA
AAA

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FIGURE 64

MPGVCDRAPDFLSPSEDQVLRPALGSSVALNCTAWVVSGPHCSLPSVQWLKDGLPLGIGGHYSLHEYSWVKANLS
EVLVSSVLGVNVTSTEVYGAFTCSIQNISSFSTLQIRAGPTSHVAAVLASLLVLLALLLAALLYVKRLNVLLWY
QDAYGEVEINDGKLYDAYVSYSDCPEDRKVFVNFILKPQLERRRGYKLFDDRDLLPRAEPSADLLVNLSRCRRLI
VVLSDAFLSRAWCSHSFREGLCRLLELTRRPIFITFEGQRRDPAHPALRLLRQHRHLVTTTTLWRPGSVTPSSDFW
KEVQLALPRKVRYRPVEGDPQTQLQDDKDPMLILRGRVPEGRALDSEVDPDPEGDLGVRGPVFGEPSAPPHTSGV
SLGESRSSEVDVSDLGSRNYSARTDFYCLVSKDDM

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FIGURE 65A

GGAGCTGGGGATCCCCGCTCTCCTGGACCCCAATGACATGGTCTCCATGAGCGTCCCTGACTGCCTCAGCATCAT
GACCTATGTGTCCCAGTATTACAACCACTTCTGCAGTCTCGCCAAGCTGGTGTCTCGCCACCCAGAAAGGGCCT
TGCACCCTGTTCCCCGCCGTCTGTAGCACCCACTCCAGTGGAAATCAGAAGATGTGGCTCAGGGCGAGGAGCTCTC
CTCAGGCAGCCTGTCAGAGCAGGGCACCGGCCAGACCCCCAGCAGCACGTGCGCAGCCTGCCAGCAGCATGTGCA
CTTGGTGCAGCGCTACCTGGCTGACGGCAGGCTGTACCATCGCCACTGCTTCCGGTGTGCGCGGTGCTCCAGCAC
CCTGCTCCCTGGGGCTTATGAGAATGGGCCTGAGGAGGGCACCTTTGTGTGTGCAGAACTGTGCCAGGCTGGG
CCCGGGGACACGGTCGGGGACCAGGCCTGGGCCCTTCTCACAGCCAAAGCAGCAGCACCAGCAGCAACTCGCAGA
AGATGCCAAGGATGTTCCAGGAGGCGGCCCCAGCTCCAGTGCTCCTGCAGGGGCTGAGGCCGATGGACCCAAGGC
CAGCCCTGAGGCCCGGCCGAGATCCCTACCAAGCCCCGGGTTCCTGGCAAACCTACAGGAGCTGGCCAGCCCCC
TGCGGGCCGCCCCACCCCTGCCCCCAGGAAGGCCTCTGAGAGCACCCACCCAGCACCACCCACGCCCCGGCCCCG
CTCCAGTCTGCAGCAGGAGAACCTGGTGGAGCAGGCTGGCAGCAGCAGCCTGGTGAACGGGAGACTGCACGAACT
GCCTGTCCCCAAGCCGAGGGGGACACCGAAGCGTCCGAGGGGACACCAGCCCCCAGGAAGGACCCCCCATGGAT
CACGCTGGTGCAGGCAGAACCAGGAAGCCAGCCCCACTTCCCCCAAGCAGCAGCCCGGGGCCACCAAGCCA
GGACAGCAGGCAGGTGGAGAATGGAGGCACCGAGGAGGTGGCCAGCCGAGCCCAACGGCCAGCCTGGAGTCCAA
ACCCATAAACCCTTTGAGGAGGAGGAGGAGGACAAGGAGGAAGAGGCTCCAGCTGCACCCAGCCTGGCCACCAG
CCCTGCCCTGGGGCACCCGGAGTCCACACCCAAGTCCCTGCACCCCTGGTACGGCATCACCCCTACCAGCAGCCC
CAAGACAAAGAAGCGCCCTGCCCCGCGCGACCCAGCGCGTCCCCACTGGCTCTCCACGCCTCCCGCCTCTCGCA
CTCGGAGCCGCCCTCGGCCACACCATCGCCAGCGCTCAGCGTGGAGAGCCTGTCGTCTGAGAGCGCCAGCCAGAC
TGCAGGTGCAGAGCTTCTGGAGCCGCCAGCTGTGCCCAAGAGCTCCTCAGAGCCTGCTGTCCATGCCCCCTGGTAC
CCCTGGAAACCTGTACGCCTCTCTACCAACTCCTCCCTGGCCTCCTCTGGGGAAGTGGAGCCTAGAGTGGAA
ACAAATGCCTCAAGCCAGCCCTGGCCTTGCCCCAGGACCAGGGGCAGCTCAGGTCCCCAGCCAGCCAAGCCCTG
CAGTGGCGCCACCCCAACGCCTCTCTTGTGGTGGAGACAGGAGCCCGGTGCCTTCCCCTGGAAGCTCGTCCCC
ACAGCTGCAGGTAAAGTCTCTCTGCAAGGAGAATCCTTTAACCAGGAAGCCATCACCTGCAGCGTCCCCAGCCAC
AAAGAAGGCCACCAAGGGATCCAAGCCAGTGAGGCCACCTGCCCTGGACACGGCTTTCCACTCATCAAACGCAA
GGTCCAGGCTGACCACTACATCCCTGAGGAGGACATCCATGGAGAGATGGATAACCATTGAGCGCCGGCTGGATGC
CCTGGAGCACCGTGGGGTGTGCTGCTGGAGGAGAAGCTGCGTGGCGGCCCTGAATGAGGGCCGTGAGGATGACATGCT
GGTGGACTGGTTCAAGCTCATCCACGAGAAGCACCTACTGGTGGCGGAGAGTCCGAGCTCATCTATGTCTTCAA
GCAGCAGAACCTGGAGCAGCGCCAGGCTGATGTGAGTATGAGCTCCGGTGCCTCCTCAATAAGCCAGAAAAGGA
CTGGACGGAGGAGGACCGGGCCCGGGAGAAGGTGCTGATGCAGGAGCTTGTGACCCTCATTGAGCAGCGCAACGC
TATCATCAACTGCCCTGGATGAGGACCGGCAGAGGGAGGAAGAGGAAGACAAGATGTTGGAAGCCATGATCAAGAA
GAAAGAGTTCCAGAGGGAGGCTGAACCTGAGGGCAAGAAGAAGGGGAAGTTCAAGACCATGAAGATGTTGAAACT
GCTAGGAAACAAACGTGATGCCAAGAGCAAGTCCCCCAGAGACAAGAGCTAACAGCACGAGAAGCCAGTTGGGGA
CTGCCCCCTCCTGGAGCAGCTCCTGGGCTGTGCTCTGTTTGAAGGGGCGCCCTGCTCCCCCTCAGATCAGTCAGG
AGGAAGATGACTAAGGGGAGGGATCCTCTGGGTGATGGCCTCTTCTCCTCAGGGACCTCTGACTGCTCTGGGCC
AAAGAATCTCTTGTCTTCTCCGAGCCCCAGGCAGCGGTGATTACAGCCCTGCCAACCTGATTCTGATGACTGC
GGATGCTGTGACGGACCCAAGGGGCAAATAGGGTCCCAGGGTCCAGGGAGGGGCGCCTGCTGAGCACTTCCGCCC
CTCACCCCTGCCAGCCCCCTGCCATGAGCTCTGGGCTGGGTCTCCGCCTCAGGGTTCTGCTCTTCCAGGCAGGCC
AGCAAGTGGCGCTGGGCCACACTGGCTTCTTCTGCCCCATCCCTGGCTCTGAGTCTCTGTCTTCTGTCTCTGTG
CAGGCGCCCTTGGATCTCAGTTTCCCTCACTCAGGAACCTCTGTTTCTGAAGTCTTCAGTTAAGTTTGTAGTTTATG
ACTGAGTGGCCTGTACTGTGACAGCTGAATGGGCCTGACGGGCAAATCCATCCCTCTCTCCCTCACAGTTCCAGG
AGCGGCTTCCCTCGTCTCCCTTACTCCACAGGGAGCCTCCCTTGCCAGGACCAGGGCTGCGACGGCCATGCTGG
GGCAGGTGAGTGTCTGTAGCTGCTCCCAGTGCTGTCCCAGGCTGCAGTTCTGGTCCCTGGTTGTGAGGTAGG
AAGGGTGCACCTGAAGCAGGTGCTCATCTCGGTTCCCTTAACGTTTATAGTCTGACCCCTCACTTAGGCTTTCCTC
TGCCACCCCGGTCCAGGGAAGAGGCTCGCTCCCGCCCATGGTCATCACTGGTCTGTCTGCTCTGTTGTCTGTCT
TTCCCTGACTCCCTCCCACCGAAGGCCTGATGGCTACTACCCCTCTGGGATGGCTATGGGAGAGGAGGAGTGAT
GGGGACCGCCACCTTTTCTGCAGGAAATGTGCCAGCAGCTCTTGGTCAAAGCACTGTTGCTATAAGCTATCTCT
GGGATGCCTCTAGGCCCCCTTCCCTCTACACACCTCTGGGAAAAGATTACACTGTATTAAGTCTCGAGGAGTTTC
CTCACCAATAAACAGACAACCTCAACTGCCAGTGCCCTGCAGCCTCGGGCCACAGCGGCAGCCTTGTTTGCCTTC

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FIGURE 65B

CCACCTGCCTCTGCCACACCTGGTGGCTGAACATCTCTGGTCGCCCAGAGGCCATGTTGGGGCCATCCTCCAAGA
GGGATCTCTGCCCTCACC GCCTGCCACTGGGCAGGATCCCTTTTCTCTGCAGGGAGAGGTGGCTCCTCGGCCATG
CAGCCCCCTGGCAGGCTCCTTCTAAACATGCCTGTTGACCTGGAGCTGGCGCCACCAACTCCAGGGCCTTTCCAGG
GCCAGACAGGTAAACACGCATGAACCCGAGTGACAGCTCTGACGGGCTGTTTCGGTGT CAGGAGACAAAGCTGGCA
GGGGCAGGGGTGAACTGGAGGCAAGTCAAGTCACCTGTGGCCTGTGGGGCTGAATGTGGGCCCCGGTGTGGCCAGA
TCCTTTGT CATAAGAAGCTAGAAATCCAGATTTTATGTGTGTGTAATTTGTAAATGCTGAAAGCTAGCCTGAATT
TTTTTTTTTTTTTTTGGAGACAGAGTCTCGCTCTGTGCGCCAGGCTGGAGTGCAGTGGCGCGATCTCAGCTCACTGC
AGGCTCCGCCTCCTGGGTTCACGCCATCCTCCTGCCTCGGCCTCCTGAGCAGCTGGGACTACAGGCGCATGCTAC
GACGCCTGGCTAATTTTTTTGTATTTTATGTAGAGACGGGGTTTCACCGTGTTAACAGGATGGTCTCGATCTCCT
GACCTTGTGATCCACCCACCTTGGCCTCCCAAAGTGCTGGGATTACAGGCGTGAGCCACCACGCCCGGCCACTAG
CCTGAATTTCAATCAAGGGTTGGCTGATACTGTGTGTCCAGGGTGGACTGGATTTGTCTGGGGGGTTCTCTGGT
TTGCTGCCTCCTGACCACATGATGGGGCCTTCGAGGTGAGGACAACTGTTCCCATTAGATTGCACCTCTGCC
TCAGGTTCTTGAGGGTGTGTGGACACAGAGGCTTTCCATGGGATGTCCCTGAGCCGGCCCTTGATTGGGGCCTCA
CCATTTACAGGGCCGTTTTATTCTGCAAACCGAAACTTGGGTGATGTGACCTGATGGGATTATGGGACTCCCTCC
AGGTGCCCCGAGACAAGGTTGATATTTCCAAAATATTTTGGTGATTTAGTGGGACAAGCAAATGACAGAATACCGG
AGAAGGCAGGGATCGTGGGTGTCAGGAGCCAGAGGGGAGGGGGACAGATGTGCTGTGTACAGGACAAGGTGTCAG
GTGACTCCTTCCCAGCAGGGCCTCGCAGATGCACAAGCACGGAGCTGGTGGGTTTTGCCCCAAGAAAGGTCACGCG
GCACATGCAGGGATTGGAACCTCCAGGCCAGGGCTCTAGGTCGCTCCACCTTTTCATGTTTCTTTCTGTGGCCA
TGGGTATAGTGAAAAGACATAAAGCTAAAGCCAACCTTTTAATCCTGAATGCACCTGCTTGCCAGGTAAATGCCCTT
GGTTGTGGTATCTTGTGAGACTTAGTTTTACAGAGGGATAATGAACCGTTGCAGAGGTTTATTGAGATCATT
ACAGAGTGGAATTCAGCACCTGCCACTGCACTCCAGCCTGGGCGACAGAGCAAGACTCAGTCTCAAAAAAAAAA
AAATTAGCTGGGCAGGGCATGGTGATGGTGCCTGTAATCCTAGCTACTTGGGAGGCTGAGGCATGAGAATTGCCT
GAACCCAGGAGGTGGAGGTTGCAGTGAGCCGAGATCGTGCCACTGTACTCCAGCCTGGGTGACAGCGCGAGACTC
CGTCTCAAAAAAAGCTGGGTGTGGGGAACACCTGTGGTCCCAGCTATTCTGGAGACTGAGGCAGGAGGATTGCTT
GAGCTCAGGAGTTCTGGCTGCAGTGAGCTATGATCATGCCACTGTATTACAGAATGGGTGACAGAATGAGAGCGA
CACTGTCTCAAAAAAAAAAAAAAAAAAAGGCCGGGAGCGGTCGTTTGTGCCTGTAATCCCAACACTTTGGGAGGC
CAGGGTGGGCGGATCACTTGAGGCCAGGAGTTCAAGACCAGCCTGGCCAACATGGTGAATCCCCATCTCTACTAA
AAAAATTAACCTGGACATGGTGGTGGACACTTGTAATCCCAGCTACTCAGGAGGCTGACACATGAGAATTGCTTGA
ACCCGGGAGGCGGAGGTTACAGTGAGCCGAGATAGCACCACTGCACTCCAACCTGGGCACAGAGTAAGGCTCTGT
CTTT

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FIGURE 66

ELGIPALLDPNDMVSMSVPDCLSIMTYVSQYYNHFCSPGQAGVSPFRKGLAPCSPPSVAPTPVESEDVAQGEELS
SGSLSEQGTGQTPSSTCAACQQHVHLVQRYLADGRLYHRHCFRCRRCSSTLLPGAYENGPEEGTFVCAEHCARLG
PGTRSGTRPGPFSQPKQQHQQQLAEDAKDVPGGGPSSAPAGAEADGPKASPEARPQIPTKPRVPGKLQELASPP
AGRPTPAPRKASESTTPAPPTPRPRSSLQQENLVEQAGSSSLVNGRLHELPVVKPRGTPKPSEGTPAPRKDPPWI
TLVQAEPKKKPAPLPSSSPGPPSQDSRQVENGGTEEVAQPSPTASLESKPYNPFEEEEEDKEEEAPAAPSLATS
PALGHPESTPKSLHPWYGITPTSSPKTKKRPAPRAPSPASPLALHASRLSHSEPPSATPSPALSVESLSSESASQT
AGAEELLEPPAVFKSSSEPAVHAPGTPGNFVSLSTNSSLASSGELVEPRVEQMPQASPGLAPRTRGSSGPQPAKPC
SGATPTPLLLVGDRSPVPSPGSSSPQLQVKSSCKENPFNRKPSPAASPATKKATKGSKPVRPPAPGHGFPLIKRK
VQADQYIPEEDIHGEMDTIERRLDALHHRGVLLLEKLRGGLNEGREDMLVDWFKLIHEKHLLVRRESELIYVFK
QQNLEQRQADVEYELRCLLNKPEKDWTEEDRAREKVLMOELVTLIEQRNAIINCLDEDQREEEEDKMLEAMIKK
KEFQREAEPEGKKKGKFKTMKMLKLLGNKRDAKSKSPRDKS

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FIGURE 67

CTTTGTTTTGCTTCGAGATGGCTGCGGGGATGTATTTGGAACATTATCTGGACAGTATTGAAAACCTTCCCTTTG
AATTACAGAGAAACTTTTCAGCTCATGAGGGACCTAGACCAAAGAACAGAGGACCTGAAGGCTGAAATTGACAAGT
TGGCCACTGAGTATATGAGTAGTGCCCGCAGCCTGAGCTCCGAGGAAAAATTGGCCCTTCTCAAACAGATCCAGG
AAGCCTATGGCAAGTGCAAGGAATTTGGTGACGACAAGGTGCAGCTTGCCATGCAGACCTATGAGATGGTGGACA
AACACATTCGGCGGCTGGACACAGACCTGGCCCGTTTTGAGGCTGATCTCAAGGAGAAACAGATTGAGTCAAGTG
ACTATGACAGCTCTTCCAGCAAAGGCCAAAAGAAAGGCCGGACTCAAAGGAGAAGAAAGCTGCTCGTGCTCGTT
CCAAAGGGAAAACTCGGATGAAGAAGCCCCAAGACTGCCCAGAAGAAGTTAAAGCTCGTGCGACAAGTCCTG
AGTATGGGATGCCCTCAGTGACCTTTGGCAGTGTCCACCCCTCTGATGTGTTGGATATGCCTGTGGATCCCAACG
AACCACCTATTGCCTTTGTCACCAGGTCTCCTATGGAGAGATGATTGGCTGTGACAACCCTGATTGTTCCATTG
AGTGGTTCCATTTTGCCTGTGTGGGGCTGACAACCAAGCCTCGGGGGAAATGGTTTTGCCACGCTGCTCCCAAG
AACGGAAGAAGAAATAGATAAGGGCCTTGGAATCCAACACAGTTTCTTCCACATCCCCTGACTTGGGCTAGTGGG
CAGAGGAATGCCTGTGCTGGGGCCAGGGGTTCAAGGAGGAGTGGATGGCACAGTGCTGTTCATCCCTTCTCCTCCC
CTCTCCCCACTCCCGGTGCTGAGGCTGCATCAGACCCTGGTAGGGAGGGGTGCCGCAGCCACTAACGGTATGTGC
TCTCCTTCAGCCCTCTCCTTCGGAGGGACGTGGTCTTGCCCACTGTCCTTTTGCCTCCATGCTGAGGTCGGTGCT
GTATTTTCAGAGGGAGGGTCCTTTTCATTCTCCTTGCTTTGTATTTAAGGACTGGGGCATAGCATGGGGGCAGTCC
CCCAGACCTCTTCATTCCCCCTCCTGTGGTGAGGGCTAGGTGTGATCAACACTTTTCTTCTCCATTCCCTTCCTG
CTTTTTTCATGGTGGGGATCCACCAGGTCACTAGCTCTGGCCCTAGTTGAAGGGCACCCCTTCCTCTGTGCCAA
GAGGATTCATCCTGGGAGAGGGGGCAAGGTGGAATGCAGATAACTCACATGTAAAAGGAACTTGGGTAGGTAAAT
AAAAGCTATACATGTTGAAAAAAAAAA

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FIGURE 68

MAAGMYLEHYLDSIENLPFELQARNFQLMRDLDQRTEDLKAEIDKLATEYMSSARSLSSSEKLLALLKQIQEAYGKC
KEFGDDKVQLAMQTYEMVDKHIRRLDIDLARFEADLKEKQIESDYDSSSSKGKKKGRTQKEKKAARARSKGKNS
DEEAPKTAQKKLKLVRTSPEYGMPSVTFGSVHPSDVLDMPVDPNEPTYCLCHQVSYGEMIGCDNPDCSIEWFHFA
CVGLTTKPRGKWFCPRCSQERKKK

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FIGURE 69

TACGTGAAGCACCGACACAAACTGGAGAATGGTCTGGCTGCGCTCAGTCCCTTAAGCAAGGGCTCC**ATGG**AGGCT
GGCCCTTACCTGCCCCGAGCCCTGCAGCAGCCTCTGGAACAGCTGACTCGGTATGGGCGGCTCCTGGAGGAGCTC
CTGAGGGAAGCTGGGCCTGAGCTCAGTTCTGAGTGCCGGGCCCTTGGGGCTGCTGTACAGCTGCTCCGGGAACAA
GAGGCCCCGTGGCAGAGACCTGCTGGCCGTGGAGGCGGTGCGTGGCTGTGAGATAGATCTGAAGGAGCAGGGACAG
CTCTTGCAATCGAGACCCCTTCACTGTCACTCTGTGGCCGAAAGAAGTGCCTTCGCCATGTCTTTCTCTTCGAGCAT
CTCCTCCTGTTTCAGCAAGCTCAAGGGCCCTGAAGGGGGGTGAGAGATGTTTGTGTTTACAAGCAGGCCTTTAAGACT
GCTGATATGGGGCTGACAGAAAACATCGGGGACAGCGGACTCTGCTTTGAGTTGTGGTTTCGGCGGCGGCGGTGCA
CGAGAGGCATACACTCTGCAGGCAACCTCACCAGAGATCAAACCTCAAGTGGACAAGTTCTATTGCCAGCTGCTG
TGGAGACAGGCAGCCCAACAAGGAGCTCCGAGTGCAGCAGATGGTGTCCATGGGCATTGGGAATAAACCCCTTC
CTGGACATCAAAGCCCTTGGGGAGCGGACGCTGAGTGCCCTGCTCACTGGAAGAGCCCCAGAAACACTTGACTCT
TCTGGAGATGTGTCCCCAGGACCAAGAAACAGCCCCAGCCTGCAACCCCCCACCCTGGGAGCAGCACTCCCACC
CTGGCCAGTCGAGGGATCTTAGGGCTATCCCGACAGAGTCATGCTCGAGCCCTGAGTGACCCACCACGCCTCTG
TGACCCTGGAGAAGATCCAGAACTTGCCTGCAGCTTCTCCTCTCAGCACACTTTGGGCTGGGATGGCAGTGGGGCA
TAATGGAGCCCTGGGCGATCGCTGAATTTCTTCCCTCTGCTTCCCTGGACACAGAGGAGGTCTAACGACCAGAGTA
TTGCCCTGCCACCACTATCTCTAGTCTCCCTAGCTTGGTGCCCTTCTCCTGCAGGAGTCAGAGCAGCCACATTGCT
TGCCCTTCATACCCTGGAGGTGGGGAAGTTATCCCTCTTCCGGTGCTTTCCCATCCTGGGCCACTGTATCCAGGAC
ATCACTCCCATGCCAGCCCTCCCTGGCAGCCCATGTTCTCCTCTTTTCTCACCCCTGACTTTCCCTGAGAAGAA
TCATCTCTGCCAGGTCAACTGGAGTCCCTGGTGACTCCATTCTGAGGTGTCACAAGCAATGAAGCTATGCAAAACA
ATAGGAGGGTGTGACAGGGGAACCGTAGACTTTATATATGTAATTACTGTTATTATAATACTATTGTTATATTAA
ATGTATTTACTCACACTTTGCCTCT

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FIGURE 70

MEAGPYLPRALQQPLEQLTRYGRLLLEELLREAGPELSSECRALGAAVQLLREQEARGRDLLAVEAVRGCEIDLKE
QGQLLHRDPFTVICGRKKCLRHVFLFEHLLLF SKLKGPEGGSEM FVYKQAFKTADMGLTENIGDSGLCFELWFRR
RRAREAYTLQATSPEIKLKWTS SIAQLLWRQAAHNKELRVQQMVSMGIGNKPF LDIKALGERTLSALLTGRAPET
LDSSGDVSPGPRNSPSLQPPHPGSSTPTLASRGILGLSRQSHARALSDPTTPL

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FIGURE 71

CTTTCTGCCCCGACTCCCACAGCTACACCATGCAGGAATTGCCCCGGCGTTACTTCCGGAGGTCCCAGGCCTTGCT
GGGCCAGACTGATGGAGGTGCCGCAGGAAAGGACACGGACAGCCTGGTGAGTACACCAAGGCTCCCATCCAGGA
GTCGCTCCTCAGCCTCAGTGATGATGTGAGCAAGCTGGCTGTAGCCAGCTTCCTGGCCCTGATGCGGTTTATGGG
TGACCAGTCCAAGCCCCGGGGCAAGGATGAGATGGATCTGCTCTATGAACTGCTGAAGCTGTGCCAGCAGGAGAA
GCTGAGGGATGAGATTTACTGCCAGGTTATCAAGCAGGTCACGGGACACCCCCGGCCGGAACACTGCACTCGAGG
CTGGAGCTTCCTCAGCCTTCTCACAGGCTTCTTCCCCCGTCCGACCAGGCTGATGCCCTACCTGACCAAGTTTCT
GCAGGATTCAGGCCCCAGCCAAGAGCTGGCCCGGAGCAGCCAGGAGCACCTCCAGCGCACAGTCAAATATGGGGG
GCGCCGGCGGATGCCCCACCGGGTGAAATGAAGGCTTTCTGAAAGGACAAGCGATTGCGCTGCTTCTTATTCA
CCTGCCGGGGGTGTGGATTATAGGACGAATATCCAGACTTTCACAGTAGCAGCAGAAAGTGCAGGAGGAGCTGTG
CCGGCAAATGGGTATCACGGAGCCTCAGGAAGTGCAGGAATTGCGCCTCTTCTCATCAAAGAGAAGAGCCAGCT
GGTGCGGCCCTGCAGCCCGCCGAATGCCTCAACAGCGTGGTAGTGACCAGGACGTGAGCCTGCACAGCCGGCG
GCTCCACTGGGAGACCCCCACTGCACTTCGATAACTCCACCTACATCAGCACCCACTACAGCCAGGTGCTGTGGGA
CTACCTTCAGGGGAAGCTGCCAGTCAGCGCCAAGGCAGACGCGCAGCTCGCCAGGCTGGCCGCCCTGCAGCACCT
CAGCAAGGCCAACAGGAATACCCCCCTCAGGGCAGGACCTGCTAGCTTACGTGCCAAAGCAGCTGCAACGGCAGGT
GAACACGGCCTCCATCAAGAACCTGATGGGTGAGGAGCTGAGACGGCTGGAAGGACACAGCCCCAGGAAGCACA
GATCAGCTTCATCGAGGCCATGAGCCAGCTGCCCCTCTTCGGCTACACCGTCTATGGGGTGCTGCGAGTGAGCAT
GCAGGCCCTGTCCGGACCCACTCTCCTGGGGCTCAACCGCCAGCATCTCATCCTCATGGACCCAGCTCCCAGAG
CCTGTACTGCCGCATTGCCCTGAAGAGCCTGCAGCGGCTCCACCTGCTAAGCCCTCTGGAGGAGAAGGGGCCCCC
TGGCCTGGAAGTCAACTATGGCTCAGCTGACAACCCCCAGACCATCTGGTTTGAGCTGCCACAGGCCCAGGAGCT
GCTATACACCACTGTCTTCTGATAGACAGCAGTGCTCTTGCACTGAGTGGCCAGCATCAACTAGAGGAGTG
CAGGCCGGGGAGAGAAGAGGATGAGGCCTCCCCGGCCCAAGTCTCACCCACATGGTCTGCCTTGGATGCTATCA
GATCACTGTTCTAGAACCTGCCTCAGCACAGCCAGCCGGCCACATGCAGGCCATGAGGCAGGGGCTGCTATCA
CGTCACCAGCAGGCAAAGAAAACAGCCAGACCCTCTCCAGGACGGCCTGGGGCCAAAGCGGGCTGCAGGAACTCG
GCTGGGGCACCTGAGGTTGCCCAGTCTGAGGGAGATGCCCACCCGACCCAGGCTCCGCCCAGGCCCCACATTAG
CACAAGCCCAGGCATGGGAGAAACAGCTGCTGAGGAAATAAACTCCCTGGAGAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAA

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FIGURE 72

MQEFARRYFRRSQALLGQTDGGAAGKDDTSLVQYTKAPIQESLLSLSDDVSKLAVASFLALMRFMGDQSKPRGKD
EMDLLYELLKLCQQEKL RDEIYCQVIKQVTGHPRPEHCTRGWSFLSLLTGFFPPSTRLMPYLT KFLQDSGFSQEL
ARSSQEHLQRTVKYGGRRRMPPPGEMKAFLKGQAIRLLLLIHLPGGV DYRTNIQTFTVAAEVQEELCRQMGITFPQ
EVQEFALFLIKEKSQ LVRPLQPAECLNSVVVDQDVSLHSRRLHWETPLHFDNSTYISTHYSQVLWDY LQGKLPVS
AKADAQLARLAALQHLSKANRNTPSGQDLLAYVPKQLQRQVNTASIKNLMGQELRRLEGHSPQEAQISFIEAM SQ
LPLFGYTVYGVL RVSMQALSGPTLLGLNRQHILMDPSSQSLYCR IALKSLQRLHLLSPLEEKGPPGLEVNYGSA
DNPQTIWFELPQAQELLYTTVFLIDSSASCTEWPSIN

[illegible]

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FIGURE 74

MALETPTPGPPREGQSPASQAGTQHPPAQATAHSQSSPEFKGSLASLSDSLGVSVMATDQDSYSTSSTEEELEQF
SSPSVKKKPSMILGKARHRLSFASFSSMFHAFLSNNRKLYKKVVELAQDKGSYFGSLVQDYKVYSLEMMARQTSS
TEMLQEIRTMMTQLKSYLLQSTELKALVDPALHSEEELEAIVESALYKCVLKPLKEAINSCLHQIHSKDGSLQQL
KENQLVILATTTTDLGVTTSVPEVPMMEKFLQKFTSMHKAYSPEKKISILLKTCKLIYDSMALGNPGKPYGADDF
LPVLMYVLARSNLTEMLLNVEYMMELMDPALQLGEGSYLLTTTYGALEHIKSYDKITVTRQLSVEVQDSIHRWER
RRTLNKARASRSSVQDFICVSYLEPEQQARTLASRADTQAQALCAQCAEKFAVERPQAHRLFVLVDGRCFQLADD
ALPHCIKGYLLRSEPKRDFHFVYRPLDGGGGGGGSPCLVVREPNFL

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FIGURE 75

ACGAGGGACGCAGCCATGGCGGAGGCGGCTTTGGAAGCCGTGCGGAGCGAGTTACGAGAATTCCCGGCCGCTGCA
AGGGAGCTCTGCGTGCCCTCTTGCTGTGCCCTACCTGGACAAACCCCCAACTCCGCTCCACTTCTACCGGGACTGG
GTCTGCCCCAACAGGCCGTGCATTATCCGCAACGCTCTGCAGCACTGGCCGGCCCTCCAGAAGTGGTCCCTCCCC
TATTTAGAGCCACAGTGGGCTCCACAGAGGTGAGTGTGGCCGTGACCCAGATGGTTACGCGGATGCCGTGAGA
GGGGATCGCTTCATGATGCCAGCTGAGCGCCGCTGCCCCGTGAGCTTCGTGCTGGATGTGCTGGAGGGCCGGCC
CAGCACCTTGAGTCCCTCTATGTGCAGAAGCAGTGTCTCAACCTGCCAGCGAGCTGCCCCAGCTGCTGCCTGAT
CTGGAATCCCATGTGCCCTGGGCCTCCGAAGCCCTGGGAAAGATGCCCGATGCTGTGAACCTTCTGGCTGGGGGAG
GCGGCTGCAGTGACTTCTTTGCACAAGGACCACTATGAGAACTCTACTGCGTGGTCTCAGGAGAGAAGCATTTT
CTGTTCCATCCGCCAGCGACCGGCCCTTCATCCCCTATGAGCTGTACACGCCGGCAACCTACCAGCTAACTGAA
GAGGGCACCTTTAAGGTGGTGGATGAAGAGGCCATGGAGAAGGCAGAGGTGTCCAGGACCTGCCTGCTCACGGTT
CGTGTCTGTCAGGCCCATCGCCTACCCTCTAAGGACCTAGTGACCCCTCTGACTGCTACGTGACTCTCTGGCTG
CCCACGGCCTGCAGCCACAGGCTCCAGACACGCACGGTCAAGAACAGCAGTAGCCCTGTCTGGAACCAGAGCTTT
CACTTCAGGATCCACAGGCAGCTCAAGAATGTGATGAACTGAAAGTCTTTGACCAGGACCTGGTGACCGGAGAT
GACCCTGTGTTGTGCTGACTGTGTTGATGCGGGGACTCTGCGGGCTGGGGAGTTCGGGCGCAGAGCTTCTCACTG
AGCCCTCAGGGTGAGGGGCGCCTGGAAGTTGAATTTGCGCTGCAGAGTCTGGCTGACCGTGGCGAGTGGCTCGTC
AGCAATGGCGTTCTGGTGGCCCGGAGCTCTCTGCTTGACGTTCAACTGGAGGAGACAGGAGACCAGAAGTCC
TCAGAGCACAGAGTTCAGCTTGTGGTTCCTGGGTCTGTGAGGGTCCGCAGGAGGCCTCTGTGGGCACTGGCACC
TTCCGCTTCCACTGCCAGCCTGCTGGGAGCAGGAGCTGAGTATTCGCTGCAGGATGCCCCGAGGAGCAACTA
AAGGCGCCACTGAGTGCCCTGCCCTCTGGTCAAGTGGTGAGGCTTGTCTTCCCCACGTCCAGGAGCCCCTGATG
AGAGTGAGCTGAAAAAAGAAGCAGGACTGAGGGAGCTGGCCGTGCGACTGGGCTTCGGGCCCTGTGCAGAGGAG
CAGGCCCTTCTGAGCAGGAGGAAGCAGGTGGTGGCCGCGGCCCTTGAGGCAGGCCCTGCAGCTGGATGGAGACCTG
CAGGAGGATGAGATCCCAGTGGTAGCTATTATGGCCACTGGTGGTGGGATCCGGGCAATGACTTCCCTGTATGGG
CAGCTGGCTGGCCTGAAGGAGCTGGGCCTCTTGGATTGCGTCTCCTACATCACCGGGGCCCTCGGGCTCCACCTGG
GCCTTGGCCAACCTTTATGAGGACCCAGAGTGGTCTCAGAAGGACCTGGCAGGGCCCACTGAGTTGCTGAAGACC
CAGGTGACCAAGAACAAGCTGGGTGTGCTGGCCCCCAGCCAGCTGCAGCGGTACCGGCAGGAGCTGGCCGAGCGT
GCCCCGCTTGGGCTACCCAAGCTGCTTACCAACCTGTGGGCCCTCATCAACGAGGCGCTGCTGCATGATGAGCCC
CATGATCACAAGCTCTCAGATCAACGGGAGGCCCTGAGTCATGGCCAGAACCCTCTGCCATCTACTGTGCCCTC
AACACCAAAGGGCAGAGCCTGACCACTTTTGAATTTGGGGAGTGGTGCGAGTTCTCTCCCTACGAGGTGCGCTTC
CCCAAGTACGGGGCCTTCATCCCCTCTGAGCTCTTTGGCTCCGAGTTCTTTATGGGGCAGCTGATGAAGAGGCTT
CCTGAGTCCCGCATCTGCTTCTTAGAAGGTATCTGGAGCAACCTGTATGCAGCCAACCTCCAGGACAGCTTATAC
TGGGCCTCAGAGCCCAGCCAGTTCTGGGACCGCTGGGTGAGGAACCAGGCCAACCTGGACAAGGAGCAGGTCCCC
CTTCTGAAGATAGAAGAACCACCCTCAACAGCCGGCAGRATAGCTGAGTTTTTACCAGATCTTCTGACGTGGCGT
CCACTGGCCCAGGCCACACATAATTTCTGCGTGGCCTCCATTTCCACAAAGACTACTTTTACGATCCTCACTTC
TCCACATGGAAAGCTACCACTCTGGATGGGCTCCCCAACCAGCTGACACCCTCGGAGCCCCACCTGTGCCTGCTG
GATGTTGGCTACCTCATCAATACCAGCTGCCTGCCCCCTCTGCAGCCCACTCGGGACGTGGACCTCATCTGTCA
TTGGACTACAACCTCCACGGAGCCTTCCAGCAGTTGCAGCTCCTGGGCCGTTCTGCCAGGAGCAGGGGATCCCCG
TTCCCACCCATCTCGCCAGCCCCGAAGAGCAGCTCCAGCCTCGGGAGTGCCACACCTTCTCCGACCCCACTGC
CCCGGAGCCCCCTGCGGTGCTGCACTTTCTCTGGTTCAGCGACTCCTTCCGGGAGTACTCGGCCCTGGGGTCCGG
CGGACACCCGAGGAGGCGGCAGCTGGGGAGGTGAACCTGTCTTATCGGACTCTCCCTACCACTACACGAAGGTG
ACCTACAGCCAGGAGGACGTGGACAAGCTGCTGCACCTGACACATTACAATGTCTGCAACAACCAGGAGCAGCTG
CTGGAGGCTCTGCGCCAGGCAGTGCAGCGGAGGCGGCAGCGCAGGCCCACTTGATGGCCGGGGCCCCCTGCCACCC
CTAACTCTCATTATTCCCTGGCTGCTGAGTTGCAGGTGGGAACTGTATCACGCAGTGCTTCAGAGCCTCGGGC
TCAGGTGGCACKGTCCCAGGTCCAGGCTGAGGGCTGGGAGTCCCTTGCGCCTCAGCAGTTTGAGTGGGGTAA
GGAGGCCAAGCCATTTGTGTAATCACCCAAAACCCCCCGCCTGTGCCTGTTTTCCCTTCTGCGCTACCTTGAG
TAGTTGGAGCACTTGATACATCACAGACTCATACAAAAA

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FIGURE 76

MAEAALAVRSELREFPAAARELCVPLAVPYLDKPPTPLHFYRDWVCPNRPCIIRNALQHWPALQKWSLPYFRAT
VGSTEVSVAVTPDGYADAVRGDRFMMPAERRRLPLSFVLDVLEGRAQHPGVLYVQKQCSNLPSELQQLLPDLESHV
PWASEALGKMPDAVNFWLGEAAAVTSLHKDHYENLYCVVSGEKHFLFHPPSDRPFIPYELYTPATYQLTEEGTFK
VVDEEAMEKAEVSRCTCLLTVRVLQAHRLPSKDLVTPSDCYVTLWLPTACSHRLQTRTVKNSSSPVWNQSFHFRIH
RQLKNVMELKVFDQDLVTGDDPVLSVLF DAGTLRAGEFRRESFSLSPQGEGRLEVEFRLQSLADRGEWLVSNGL
VARELSCLHVQLEETGDQKSSEHRVQLVVPGSCEGPQEASVGTGTFRFHCPACWEQELSIRLQDAPEEQLKAPLS
ALPSGQVVRLVFPTSQEPLMRVELKKEAGLRELAVRLGFGPCAEEQAFLSRRKQVVAALRQALQLDGDLOEDEI
PVVAIMATGGGIRAMTSLYGQLAGLKLGLLDCVSYITGASGSTWALANLYEDPEWSQKDLAGPTELLKTQVTKN
KLGVLAPSQLQRYRQELAERARLGYPSCTNLWALINEALLHDEPHDHKLSQREALSHGQNPLPIYCALNTKGQ
SLTTFEFGEWCEFSPIYEVGFPHYGAFIPSEFGSEFFMGQLMKRLPESRICFLEGIWSNLYAANLQDSLYWASEP
SQFWRWRVNQANLDKEQVPLLKIEEPPSTAGRIAEFFTDLLTWRPLAQATHNFLRGLHFHKDYFQHPHFSTWKA
TTLDGLPNQLTPSEPHLCCLLDVGYLINTSCLPLLQPTRDVLILSLDYNLHGAFQQLQLLGRFCQEQQIPFPPI
PSPEEQLOPRECHTFSDPTCPGAPAVLHFPLVSDSFREYSAPGVRRTPEEAAAGEVNLSSSDSPYHYTKVTYSQE
DVDKLLHLTHYNVCNNQEQLLEALRQAVQRRRQRRPH

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FIGURE 77A

CCAGACAGCCTTGTATGGGAAGATGGGAAGGGTGAGGTGCGCCACATCCTTATGGGCACCGGAAGTTCATCACTAT
GTCTGATGGAGCCACTTCTACATTGACCTCTTCGAGCCCTTGCTGAGCACTGTGTTGGAGATGATATCACCAT
GGTCATCTGCCCTGGAATTGCCACACAATTCAAAGTTGGATCTTGAGTTTGGAGAAAGATATTTCCAACCTAAGT
GGGTACTATTTTGAACAGATTTTTAATTTAATAGCCTATATTTGTAGTCTGTTGGATAGGTGTTTCCAAAGTG
TGTCTTCTCAAGTGAAAACGCAACTCTAGGTTTCAAGTACTCCTTTTCTCCGATCCTGTGGTACTTGAATATCCA
AAAACCTGCACTTTGAACAATCAGCTGTTGCTATCTGGAACATAACAGAACTATGAGTAAAATTGCCTGGATAC
TTTAAAAAGATATTTTTCTCCTTCATCTCCTTTGACTCCAGGACAGACTGGAATATAAGTAGTGGGTCTGCATG
GATGTTTCAGGGATCAAAGGAGCCACCTGGGCGCCTGAGTGCCAAACCTCAGGGCCACAGGTGGGTGTGGTTTGG
GCACGGGTCCAAGTGACTGTGACGGGACCCCTGGGCATGGGGCCAGGTCTGTAACCTGAAGAAGTTGTTTTCTGA
CAATCACCAAATCATCCGAATGACATCAAAGCAGCCCTTATCTCAGAGACCGAGATTTCTGTGGTCTCAACTTC
GCTTTGGTATAATTTCTGGCACTCACCAGCCTCTATCATTATGACTTTCCCCCAGTGTATTATTTCTCTAATAG
GTTTTCTTTTACGTTCTTTTAGCACAGACTGGCACTTTACCCCTCTCAATTTGGAAGTTAGCCCCTCTCCTCTGT
TACTTTTCCCTTCACCCAACCTACAGCTGTGATCTAGAACATTCATAGTCATATTTCTGCTACTACTACCTTCATT
TATCAAGACTTTTTATGAGAATAGGTAAACCAAGCAATAACTTCCTAGGACTGAATCACCACCCAGAAAGAGCGA
GAGGCTCCTTTTCATATGCCTGAGGCCACACCCCTTAACCTGTTCTGACAAAATAGTGGCTGGCCCATGTACCAGC
TCCATTGAGAAATTCAGGAAGAGAAAAGACAGCCCTGTTGTACACAAAACCGGTGTGGGGGAGGGTGGAGCCTGG
TCTGCACGGCAGTCTGTTGGTGGCCCTGTGGAGGACAGGCAGGGCTGGCAGCATAGCCTTTGTTGCCACACAACCG
GAATTTGCTCCCCAGGACTGTGGGAGCCAGTGTCCCAGCTGAAATCTTTTTAGTGTGTGGCTCTGAATGGCACT
CACATTCCATTTTGGCTCACATGAAACTAACTGAAGCCCTTTGTTCAAGCTTCAGGCTCTTAGGCATGGAAATGA
GAATGTGACTGTGGCTGTCTTACAGGAAAATTCTTGTGTTGTCCCTGAATGAGAGCACAGAGGCATTGAATTCACA
GAGCTGCAAACTTGCTGATAAATGAGGGAGTGGCAGTTTATAGATAGGTCACTTTTTTCTTCTCCAGGTGT
CCTTGCCCTTCTTCCCAAAGTCATTCATTTCTGATGAGTATATGAATCCCCCTCTTGCTAGTAAGGTTCTATTTG
GGCTAAAACAAGGCTGAATTTTTAAAGAGTATTTGAATATATTTTAGAATCAAATTGAGGCTATAAATTGCATCA
ATCTGGACAATTCATTGCAGGAATAATATGTTAAAAACCAATGGGGAGAAGCACCCACATCTCTCCTGTAGCAC
TCCGTGTCTCATAAGCAATTTGAAGACACTTACAAGTAACTGATTCCAGTCAAATTAGGATTAAGTACTCAAAA
AATGGTGTCAAGTTTCTTTAATGTTTTATGTTAGAAGTGAGTTTAAACAGACTTGAAGAAAACCTGTTATCTTTTC
CTGCTGTGAGTTTACACAAATGATTCCAGAGCAGAAATGAAAGCAGAAAGCTGTTGGTTACAATATTCTTTTAACC
TCTCTGCAGCATTTTACACTTACTGGGAACCTTATGATTCACCGTAAGAGTGGAAATATACCTGAGTTCGTGTCC
TAATGGTCTCTAATTCACATTGGATCGTGGGCAAATCACCTCACCTCTCTGAGCCTGTTCCCTCCTCTTAGACCA
TCTCTAAGACCACTTCATCTATTTACACATCATTGCTTGAACATTGCTGAACATCTGCGTGAACCTTGGCCTCTC
CAGCCCTTGACAGGTGGAAACAGCTGTGTCAAGGCTCAAGGCTCACGCTGAGGGGACTTGGAGGGAGGGGGCTTCT
GCATTAAGCTTTCTGGTGAAGACCCTTGATCTTGTCCAAAGCCCTGTGTCTTTGACTGGCTTCTCTTCAGAGTC
CCCGTTGTCAATCGTAAGACCCTTGCTGTTTGGAGGGTGGTCTTGTGACTGTGGCAGCTGCTGGCCGCTGGAATGA
GGAGCCTATCTCCATCCTCCAGTGTGACTCAGGCAGAGCATTGAGAATTTCCAGGGCAGAAATCCTTCCTGCTCA
GGCTTTTCATTCTAAAACTACAGTCTTCATTAAAGCTGAACTTTCTGGGTAGCTGAGCTTATATGCCCGGCATCTG
AATGAGAGCTCTCTTTGTAAGTGTGTGACTTGAGATCTAGTTTGCCAGCTCCTGGGAAACAATACATGTGTTCTT
GTTTGTGTTTGTCTCAGCAAGCAGATGTCTGAGATGTAAGAAGCTTTTCTTTTCTGTGGCATTGATTCTGACTTA
GAGCTGAAGTAAAGATCACTGAAACATCACGTCAAGTTGAAGTCACTCATAGGTCTTTGTCTTTTAGGCAGGACA
GGAGAGTCATTAAGAAGCATTTCACTGTAGCATTCTATCACAATATCATCTGGAATTGTTTTCTTTGCCAGAAA
GCCTTAACCTGCCTCTAGAGAATCCCTGGTATTACAACGATATTGCGGCATTAGAATTCCAACTCTTCTGCTGTG
GAAGTTTGAAGCGAAGCTGCAGCAAAACAGAGAATTTCCCTCAAGTGGCCTGTAGGCTCCTTGTTATCTTATGCC
CCCACCCCTCCCTCAACAATATGAGTGATCCAGAAGTGGCCCAAACACCTCAGCTCTGGTCCCTTTTTTGCCCTTC
TTGGCCTTACTCTGTTGTTCAAAGCCACTTTGGATTGCTTGGATGCTTCGAACAGCCATGAAAAGTAGCCTGCCT
GTGGCATTAGAGGCCAAGCAATTGACAGAAAGGGTTTCTTCTACCTCTGTTATCTAAGCAGAGGGAAGTAACT
TCTCACCAGCCCCCACCCTCACTGCCCCGATTACACTAGAATTGCTTTGCGCAAATTGTAGTTGAAGCTAAGG
AAGGGGAATCTGGCCCTGCTGGGAGAGGGAAGTGAATGCCACACAAGGCAAGGCCTGCTTCCTTCCTTCCCCT
CTGCTGCTGCTGCCTCGGAACGCTGCAGCCAGGCTTCCTCCACAGTGGCCCTTGGAAGCAGGCCGAGAGTAG
ACAGCTGCTCCTTTTGAAGAGTCAGTCCCTGTGTTTCTGAACTGTTTTTCTAGCATGTATGTGGGTAGAGC

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FIGURE 77B

TTTCATGCATCTCTAGTAATAATAAGCTGAAATTAGTTTTTTTTTTAATTCTCCAATTTAAAACCTTTTAATTAAA
AAGTAAATTTTAATGTCGAAAATGCAAACCTTGGGGAGGGCAGAAAGATCACACACAAGGCTGTCAC TTCATACTT
GCAGGATTGCACAGCAGCCGGGCAGAGGCGCTCCTCACTTCCCAGATGGGGCGGCGGGCAGCAGAGACGCACCTC
ACTTCCTAGACAGTGCGGCACCAGGCACAGGCACACCTCACTTCCCAGACAGTTGGGCGGCCCAGGCAAGCGCTC
CTCACTTCCCCAGATGGGGCGGCTCCCGGGAAGCGGGCTCCCTCACTTCCCAGACAGGGTGGCCAGGCAGAGGT
GCTCCTCACTTCCCAGAACAATTCTTTATGAATTTGATAAAGGACTGAAGTGCAACTGAAAGCTGCTAGTGATGA
TCTGGTAATATACAATTTGTCCAGTAGCCAGTTTGTTTTATTGTGTTTTCTAACCATAAGAGATCATTAAAGGC
AAAGCCTGTATGACGCTGTACACACACAAAAAATGGTCACCGCAGGCCATACTACCAATGAAATGGTAGGTAAA
CAAATCTTCTGGTCAAGAGAAAAAAGAAATAGCACTCTGCATGCTTTGCTCTACAAGATGAATTTCCCTAG
AAAGAATCCAATGAAGGCCGGGCATAGTGGCTCACT

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FIGURE 78

QTALYGKMGRVRSFHPYGHRKFITMSDGATSTFDLFEPLAEHCVGDDITMVICPGIATQFKSWI

GAGATGCCTGAACCCAGCCTTGGGGAATCTCACAGCCCTCACCTACCTCAACCTCAGCCGAAACCAGCTGTGCGT
 GCTGCCACCCTACATCTGCCAGCTGCCCCTGAGGGTCTCATCGTCAGCAACAACAAGCTGGGAGCCCTGCCCC
 TGACATCGGCACCCTGGGAAGCCTGCGACAGCTTGACGTGAGCAGCAACGAGCTCCAATCCCTGCCCTCGGA
 GTGTGGCCTCTCTTCCCTGCGGGACCTCAATGTCCGGAGGAACCAGCTCAGTACGCTGCCCCGAAGAGCTGGGGGA
 CCTCCCTCTGGTCCGCTGGATTTCTCCTGTAACCGCGTCTCCCGAATCCCAGTCTCCTTCTGCCGCTGAGGCA
 CCTGCAGGTCAATTCTGCTGGACAGCAACCCTCTGCAGAGTCCACCTGCCAGGTCTGCCTGAAGGGGAACTTCA
 CATCTTCAAGTATTTGTCCACAGAGGCCGGGCAGCGTGGGTGCGCCCTGGGGGACCTGGCCCCCTTCTCGGCC
 GAGTTTCAGTCCCTGCCCTGCAGAGGATCTATTTCCGGGACATCGGTACGATGGTGGGCTGGACTCAGGCTTCCA
 CAGCGTTGATAGTGGCAGCAAGAGGTGGTCTGGAATGAGTCAACAGATGAATTTTCAGAGCTGTATTCCGGAT
 CTCAGAGCTGGCCCGGGAGCCCCGGGGGCCAGAGAACGCAAGGAGGATGGCTCAGCGGACGGAGACCCTGTGCA
 GATTGACTTCATCGACAGCCATGTCCCCGGGGAGGATGAAGAGCGAGGCACTGTGGAGGAGCAGCGACCACCCGA
 ATTAAGCCCTGGGGCAGGGGACAGGGAGAGGGCACCAAGCAGCAGGCGGGAGGAGCCGGCAGGGGAGGAGCGGCG
 GCGCCCGGACACCTTGCAGCTGTGGCAGGAGCGGGAACGCGCGCAGCAGCAGCAGCGGGGCGTGGGGGGCCCC
 GAGGAAGGATAGCCTCTTGAAGCCAGGGCTCAGGGCTGTTGTGGGAGGGGCCGCCGCGCTGTCCACTCAAGCCAT
 GCACAACGGCTCGCCTAAGTCCAGTGCCTCCCAAGCAGGGGCTGCAGCGGGGACAGGAGCCCCCGCCCCCTGCCC
 TGCTCCCAAGAGCCCCCTTCCCATAGCTGGACCAGCGACAGCACCTGCTCCACGGCCACTTGGCTCCATTAGAG
 ACCAAACAGCTTCTCTTCCGTTCTCCTCTCAGAGTGGCTCAGGCCCTTCTCACCAGACTCTGTCTGAGACC
 TCGGCGGTACCCCCAGGTTCCAGATGAGAAGGACTTAATGACTCAGCTGCGCCAGGTCCTTGAGTCCCGGCTGCA
 GCGGCCCTGCTGAGGACCTGGCCGAGGCTCTGGCCAGTGGGGTCACTCTGTGCCAGCTGGCCAACCAGCTACG
 GCCGCGCTCCGTGCCCTTTCATCCATGTGCCCTCCCCTGCTGTGCCAAAACCTCAGTGCCCTCAAGGCTCGGAAGAA
 TGTGGAGAGTTTTTCTAGAAGCCTGTGCAAAAAATGGGGGTGCTGAGGCTGACCTGTGCTCGCCCTCGGATCTCCT
 CCAGGGCACTGCCCCGGGGGCTGCGGACCGCGCTGGAGGCCATGAAGCGGGTGGGGGGCAAGGCCCTACCGCCCC
 CTGGCCCCCTCTGGTCTGGGCGGCTTCGTGCTCTTCTACGTGGTCTCATGCTGCTGCTCTATGTACCTACAC
 TCGGCTCCTGGGTTCTTAGGCCCAAAAATCGGCCCTCCCTCACCCCTTTCCCTTCTCTCTATTTATAAGGTCCC
 TGCTCCACCCGACCCACCTGCGGTGCCTTCAGCCCCAACCAAGACACTAGTGACCCCCCTTACAGACACTGA
 CCTCAGAGGCCACTCTGGTGCCTCCAGACCCTGGGCCCCCAGCCTCTGGCCTCCCTCCAGTAGCCCCACGAGT
 CCCCACCTCTCAGTGCTGACGGTGCCTTCATGTCCCCGCCGGCCCTGCCCTGCCCTCTGTACCCCGTGAGGGGT
 GGCAGGAGCTGGAGTCTCCCCCTTCTCCTGTGCCCTCCCTTCCCCCCCCAACAGCTGCTATGGGGGGGCTAAA
 TTATCTCTATTTTGTAGAGAGGATCTATATTTGTAGGGGTTCGGGGCCAGGCCGGGTCCCTATCTCTGTGTATA
 AACTGTACAGACCGTGGCCGCCCTGCTGTGTGTGTGTGTGTGCGCGCGCGCGCGCTGCTCCGCGTGTGGT
 GGCTGTGGCCATGGCTCTGTGCCACCAGCATCTCCCTCCTGAGATGCCGGCCTCTCATGCTCCCGAGCGTCCG
 CCAACCCCCCGTGTACCTCCCTTCTGTTATCGCTGACAGCTTCTTGTGCTCTATTGTGCGCGAGCCCCGAGC
 GCACGGTGATGCTCGGGTCTGCCCCGACCCCTGCCACAGGCCGGAAGCCGAGGGGGCACCGTGGGGAAGCTA
 ACCCGGCCCTTCCCCCAGGAGTCACTGTGCCAGCCCCACCACATCCTGGAAGAGGAGGGGGCCCCGGGAAGGGG
 CCTCCCTACATCGCTGCTGTGCTCCACGCCCTGCTGGACCGCCTTAGGGGTGAAGGTGGGGGCACAGGGCCCCA
 CCGCCCCGGGACCCCGGGAGCAGAAGACGCGCCTGGGCTCCGCGCTCTCAGAGAAGCACGTGGTGAGGGTGGCC
 TGGGCTGGGCACCTTGGCCTGCCGGCCTGGCTGCCTCTGGGGTTCAGGGTCTGGGTGGAAGGACCGCGGGTGT
 CGCAGGTGTGCTGTGAGCCGAATAAACAGAAGCCAGAAGCCCTCTGGGTGGCCCTCAGAAAAAAAAAAAAAAAAA
 AA

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FIGURE 80A

CTGCCCACCATCTTTGTCCCTGGCAAAGTGGGTTTTGCGCAGTGGCTTAGACCTAGAAAAGAATCGTGACGGGCA
GGAAACCATTACACCACCACCTGGGCTGTGCTCTCCGGCTCCCGCCGCCACCCCGCCCTCGCCTTCGCCTCCGC
TCCGGTGCACATTAAAGATCCAAAGT**CATG**ACTGACTCCAAGTATTTACACAACCAATAAAAAAGGAGAAATATTT
GAACTAAAAGCTGAACTCAACAATGAAAAGAAAAGAAAAGAGAAAGGAGGCTGTGAAGAAAGTGATTGCTGCTATG
ACCGTGGGGAAGGATGTTAGTTCTCTCTTTCCAGACGTAGTGAAGTGTATGCAGACTGACAATCTGGAAGTAAAG
AAGCTTGTGTATCTCTACTTGTATGAAGTACGCCAAGAGTCAGCCAGACATGGCCATCATGGCTGTAAACAGCTTT
GTGAAGGACTGTGAAGATCCTAATCCTTTGATTGAGCCTTGGCAGTCAGAACCATGGGGTGCATCCGGGTAGAC
AAAATTACAGAATATCTCTGTGAGCCGCTCCGCAAGTGCTTGAAGGATGAGGATCCCTATGTTCCGGAACACAGCA
GCAGTCTGCGTGGCAAACTCCATGATATCAATGCCCAAATGGTGGAAAGATCAGGGATTTCTGGATTCTCTACGG
GATCTCATAGCAGATTCAAATCCAATGGTGGTGGCTAATGCCGTAGCGGCATTATCTGAAATCAGTGAGTCTCAC
CCAAACAGCAACTTACTTGATCTGAACCCACAGAACATTAATAAGCTGCTGACAGCCCTGAATGAATGCACTGAA
TGGGGCCAGATTTTTCATCCTGGACTGCCTGTCTAATTACAACCCTAAAGATGATCGGGAGGCTCAGAGCATCTGT
GAGCGGGTAACTCCCCGGCTATCCCATGCCAACTCAGCAGTGGTGCTTTCAGCGGTAAAAGTCTAATGAAGTTT
CTAGAATTGTTACCTAAGGATTCTGACTACTACAATATGCTGCTGAAGAAGTTAGCCCTCCACTTGTCACTTTG
CTGTCTGGGGAGCCAGAAGTGCAGTATGTGCGCCTGAGGAACATCAACTTAATTGTCCAGAAAAGGCCTGAAATC
TTGAAGCAGGAAATCAAAGTCTTCTTTGTGAAGTACAATGATCCCATCTATGTTAACTAGAGAAGTTGGACATC
ATGATTCGTTTGGCATCTCAAGCCAACATTGCTCAGGTTCTGGCAGAAGTGAAGAATATGCTACAGAGGTGGAT
GTTGACTTTGTTTGAAGGCTGTGCGGGCCATTGGACGGTGTGCCATCAAGGTGGAGCAATCTGCAGAGCGCTGT
GTAAGCACATTGCTTGATCTAATCCAGACCAGGAGTGAATTATGTGGTCCAAGAAGCAATTGTTGTATCAGGGAC
ATCTTCCGCAAAATACCCCAACAAGTATGAAAGTATCATCGCCACTCTGTGTGAGAAGTTAGACTCGCTGGATGAG
CCAGATGCTCGAGCAGCTATGATTTGGATTGTGGGAGAATATGCTGAAAGAATTGACAATGCAGATGAGTTACTA
GAAAGCTTCTTGAGGGTTTTTCAGATGAAAGCACCCAGGTGCAGCTCACTCTGCTTACTGCCATAGTGAAGCTG
TTTCTCAAGAAACCATCAGAAACACAGGAGCTAGTCCAGCAGGTCTTGAGTTTGGCAACACAGGATTCTGATAAT
CCTGACCTTCGAGACCGGGGCTATATTTATTGGCGCCTTCTCTCAACTGACCCTGTTACAGCTAAAGAAGTAGTC
TTGTCTGAGAAGCCACTGATCTCTGAGGAGACGGACCTTATTGAGCCAACCTCTGCTGGATGAGCTAATCTGCCAC
ATTGGTTCTTTGGCCTCTGTGTATCATAAGCCTCCCAATGCTTTTGTGGAAGGAAGTCATGGAATTCATCGTAAA
CACTTGCCAATTCATCATGGGAGCACTGATGCAGGTGACAGCCCTGTTGGCACTACCACTGCAACGAACCTGGAA
CAGCCTCAGGTTATCCCTCTCAAGGTGATCTTCTAGGGGATCTTTTAAACCTTGACCTCGGTCCCCCAGTCAAT
GTGCCACAGGTGTCTCCATGCAGATGGGAGCAGTGGATCTCCTAGGAGGAGGACTAGATAGTCTGGTGGGACAA
TCCTTCATCCCATCATCGGTGCCTGCAACCTTTGCTCCTTACCTACACCTGCTGTGGTCAGCAGTGGACTGAAT
GACCTGTTTGAAGTCTCCACAGGGATAGGCATGGCACCTGGTGGATATGTGGCTCCTAAGGCTGTCTGGCTACCT
GCAGTAAAGGCTAAAGGCTTGGAGATTTCCGGAACATTTACTCACCGCCAAGGGCACATCTATATGGAAATGAAC
TTCACCAATAAAGCTCTGCAGCACATGACAGATTTTGCAATCCAGTTTAAACAAAATAGCTTTGGTGTATCCCC
AGCACTCCTCTGGCCATCCATACACCACTGATGCCAAACAGAGCATTGATGTCTCCCTGCCTCTCAATACCTTG
GGCCAGTCATGAAGATGGAACCTCTGAATAACCTCCAGGTGGCTGTGAAAAACAATATCGATGTCTTCTACTTC
AGCTGCCTCATCCCACTCAATGTGCTTTTTGTAGAAGATGGCAAAATGGAGCGCCAGGTCTTCTTGCAACATGG
AAGGATATTCCCAATGAAAATGAAGTTTCAAGTTTCAAGTAAAGGAATGTCATTTAAATGCTGACACTGTTTCCAGC
AAGTTGCAAAACAACAATGTTTATACTATTGCCAAGAGGAATGTGGAAGGGCAGGACATGCTGTACCAATCCCTG
AAGCTCACTAATGGCATTGTGATTTTGGCCGAAGTACGTATCCAGCCAGGAAACCCCAATTACACGCTGTCACTG
AAGTGTAGAGCTCCTGAAGTCTCTCAATACATCTATCAGGTCTACGACAGCATTTTGAAGAACT**TAACA**AGACTGG
TCCAGTACCTTCAACCATGCTGTGATCGGTGCAAGTCAAGAACTCTTAAGTGAAGAAATTGTATTGCTGCGTA
GAATCTGAACACACTGAGGCCACCTAGCAAGGTAGTAAGTCTAACCTGTGCTAACATTAGGGCACAACCTGT
TGGATAGTTTTAGCTTCTGTGAACATTTGTAACCACTGCTTCAGTCACCTCCACCTCTTGCCACCTGCTGCTG
CTATCTGTCTTACTTGTGGGCTTCTCCATGCTGTGCCAATGGCTGGCTTTTTCTACACCCTCTTTTGTAGTGTAG
TTTGGTATTTTGTAAATTGAGAGCTCATTTCAAAGCAGAAAAAGACAACAAATATTAAGCAAGGAAAAGTGTA
CTGAAACACTGCACTTTACTGTTTTATACTTTTGTACATATGAGAAATCAAGGGATTAGTGCAACCAAGTAGAAGG
CATTGAAATGACTGTCATTAACACACAGTCCTGGAGGCAGAGATGCAGTTACCTACCTAGCTTTTGATGGGTT
CTCTTACCTGTAGTAGCCTTATCCCTGGTCATTTGGATTTTCAGTTTGTCTTTTTTCTTTTTTCCCCCTCCAACT

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FIGURE 80B

CCTTTTCCTTGGCCAAGCCTTCATGCTTCCCCCTTTCCATATTATAATCTCATTGATTGCTCTGCAGTTGGGAA
CGGTGATCTTCTTGAATGATGTTTCAGTGTGCAAAAACCTATAGAGCCTGTCAGCACCAAAGCTGACAGAAGTTAT
ACCTTACTCCTTTCCCTTTCCCCTGAACAAACCTGCTAATCCCACTAATTCAGGAATTTGAGTAGAGATGGGGAAC
AAGAACCCAGATGCTGTCCCTCACCCTCTCCTGTATTTCTCAGGTCCAGTTCAAATCTAAAATTCTACTTTT
AGAGTTGAAACAGAGTAATAACTTATCTAACCCTCTTTTCTACAAAGGAGAAAGATAAAAGGCACAAAGGTTAC
CGCCAAGGCCCGTCAGCTGTGTAGTGGCAAAGCCGAGACCGAGTCTCCTAAGTCCCCGTCAGTGTGGTTTTTACC
ACAGGACTGTCTCTTGTCTGTTTTTCCCCTAATGCCTTCTCCTGCCTTTTCTGTGCCTAGTTTTTGGCTCTTCACAT
ATTCCATATTGATTTTGAAGCTCTGTATATTGGCATCAGGTGGCAGCTGAATATCTTTTGAATTACTCGAAGGTA
AAGCCAGATGCCAGAATGAAGGTGTAGCCAGTGTTCCTCATATGCCCTGGAGCCCCACTTATTGAGGCCAGCAG
AATAGGTGCAGAGATGAAGTGAGCTTAGAGATGTTGCAAATGCTCTTTATCCCTTCAGCTCTCTGTATCTGCTCTT
TCTTCATGATACTTAGTCTGCAGGGCATATTAAGATCATCCCAGAGGTTTCAGGCAGTTCCTGTCTCTCTGAAAA
GACTGGGGGATATGAAATCTTCCCCCTACCCCACTTAATGCGTTGGATATGATTTTTTCAAAGAATGCTTCATGCC
CAAAATACCAGCCTGTTTAGCAGTGTTACACTGTTTGATCTGCGGGCACTTGTTGCATTGCCTGGCACCCCAATAT
TCAGGGTCCATGACTAAGACTGGTCTTCTCAGATGCCCTGCTTAAATCAGGGGCACTTCAGGCTCCACAGGCGTC
ATGTTGGACTGAGACCTAACTCACTGGACTCAGAGGAGGAATCGTGGAAAACAAGAGCAAACTACCCACACCC
CTATTTTCATGTCTGAAATAACCCTGTTTCATACCAGTTGCAAAGCTTGTGGGGAGCGGTCCCACAAAGCACTTTC
TTAAACCTTGAGAATCTCCAAGAGAAAAATATTTGGGGAAGGAGGGAGGAATATGTCCCTTGACACACCACCCCT
GAAGCACATGGCAGTAGGAAACAGCATAGGATTGTATGTGGGAGGTGGATAGGTGCGGTGATGTGTGGAGCGGAAA
AGCAGGTTGGTAAAGTTCCCTTCTTGGGACTTATTCCCTGGAGTCAGTGGATACAAGTAGTGCAGAAGGTTTACAC
TGCAAATAGTGTCTCATCTCAAAGCAAACCTATCATTCCAGAAGGAAAAGTGTGTGTCAGGGCAAGCAGACAACACA
ATTTCCATATCAGAATATGTCCCTCAACCCCCGAAACAAGGCTTCTCTCAGCCTCCCCACCAGTGATGGATAACAG
CTCCTATTCTCAGCTGACCTGACTGAGCCAACCCATGAACTCTTCACTCCTTGGGGAAGCCACCTCCCATCACAC
CCCTGAGCAGAGTTAGGGAGGAATTCTACTTCCCATAAAAGGACCTCTCCTGAGAGGCAAAACCTGTTGCCTCCA
CCACGGCTTCCCTCTTGGCTCATTCCAAGCTTGGCCAAATTGGGGAAGTGGGATGGAGGTTGCCCTGCATCCCCC
CTCCTCTGCCTGAGTGTGTCTTTGTAATGTCAGCTGGCATCATACAAAGAGCAGGAGAAGCAACACCCAGAACT
CTTTTGCTGGTCAGAGATTCCCTGAGTGTCTGTCTCACCCAAGCCTGCTCTGTGTCTGTGTTGTGAAGCTTGAG
ACTCTGGAAAGAAATGGGGAGGGGGGGCAGGGGAAATGTTGCCCTAAGAATGCTTCTCATTCTCTGTCTTATT
GGGTCTGTTTTTCGGGAGGGTGGGGGTGGGGGAAGCTTGACCTTGTGTCTTCGTCAATAAACTCACATTTACA
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FIGURE 81

MTDSKYFTTNKKGEIFELKAELNNEKKEKRKEAVKKVIAAMTVGKDVSSLFPDVVNCMQTDNLELKKLVYLYLMN
YAKSQPDMAIMAVNSFVKDCEDENPLIRALAVRTMGCIRVDKITEYLCPELRKCLKDEDPYVRKTAAVCVAKLHD
INQMVEDQGFLDSLRLDIADSNPMVVANAVAALSEISESHPNNSNLLDLNPQNINKLLTALNECTEWGQIFILDC
LSNYPNKDDREAQSI CERVTPRLSHANSVVLSAVKVLKMFLELLPKDSDYNNMLLKKLAPPLVTLLSGEPEVQY
VALRNINLIVQKRPEILKQEIKVFFVKYNDPIYVKLEKLDIMIRLASQANIAQVLAELKEYATEVDVDFVRKAVR
AIGRCAIKVEQSAERCVSTLLDLIQTKVNYVVQEAIIVIRDIFRKYPNKYESIIATLCENLDSLDEPDARAAMIW
IVGEYAERIDNADELLESFLEGFHDDESTQVQLTLLTAIVKLFLLKKPSETQELVQQVLSLATQDSNPNDLRDRGYI
YWRLLSTDPVTAKEVVLSEKPLISEETDLIEPTLLDELICHIGSLASVYHKPPNAFVEGSHGIHRKHLPIHHGST
DAGDSPVGTTTATNLEQPQVIPSQGDLLGDLLNLDLGPPVNVFPQVSSMQMGAVDLLGGGLDSL VGQSFIPSSVPA
TFAPSPTPAVVSSGLNDFELSTGIGMAPGGYVAPKAVWLPVAVKAKGLEISGTFTHRQGHYMEMNFTNKALQHM
TDFAIQFNKNSFGVIPSTPLAIHTPLMPNQSIDVSLPLNTLGPMKMEPLNNLQVAVKNNIDVFYFSCLIPLNVL
FVEDGKMERQVFLATWKDIPNENELQFQIKECHLNADTVSSKLQNNNVYTI AKRNVEGQDMLYQSLKLTNGIWIL
AELRIQPGNPNYTSLKCRAPVSVQYIYQVYDSILKN

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FIGURE 82

GGCACGAGGGCGCGGAGCGGAGCGGGCGGGCGCAGCTAGCGGGTCGGCCGCGGAGCGGAGGTGCAGCTCGGCT
TCCCCCGGCACCCCTCCCCCTCGGGCGCCAGCCCCACCCCTCCGCCGGCCGGGCGGACCCCGCCGTACTATCCCC
TGCGGCGCGAGCCCGGGGCGGCTCCAAGCGCCCCCAGCAGACCCCATCATGGGCAGCCAGAGCTCCAAGGCTC
CCCGGGGCGACGTGACCGCCGAGGAGGCAGCAGGCGCTTCCCCCGCGAAGGCCAACGGCCAGGAGAATGGCCACG
TGAAAAGCAATGGAGACTTATCCCCAAGGGTGAAGGGGAGTCGCCCCCTGTGAACGGAACAGATGAGGCAGCCG
GGGCCACTGGCGATGCCATCGAGCCAGCACCCCTAGCCAGGGTGCTGAGGCCAAGGGGGAGGTCCCCCAAGG
AGACCCCAAGAAGAAGAAGAAATTCTCTTTCAAGAAGCCTTTCAAATTGAGCGGCCTGTCTTCAAGAGAAATC
GGAAGGAGGGTGGGGGTGATTCTTCTGCCTCCTCACCCACAGAGGAAGAGCAGGAGCAGGGGGAGATCGGTGCCT
GCAGCGACGAGGGCACTGCTCAGGAAGGGAAGGCCGCGAGCCACCCCTGAGAGCCAGGAACCCAGGCCAAGGGGG
CAGAGGCTAGTGCAGCCTCAGAAGAAGAGGCAGGGCCCCAGGCTACAGAGCCATCCACTCCCTCGGGGCGGAGA
GTGGCCCTACACCAGCCAGCGCTGAGCAGAATGAGTACCTAGGTAGGGGCAGGTGGGTGATCTCTAAGCTGCAAA
AACTGTGCTGTCCTTGTGAGGTCACTGCCTGGACCTGGTGCCCTGGCTGCCTTCCTGTGCCCAGAAAGGAAGGGG
CTATTGCCTCCTCCCAGCCACGTTCCCTTTCTCCTCCTCCTCCTGTGGATTCTCCCATCAGCCATCTGGTTCTC
CTCTTAAGGCCAGTTGAAGATGGTCCCTTACAGCTTCCCAAGTTAGGTTAGTGATGTGAAATGCTCCTGTCCCTG
GCCCTACCTCCTTCCCTGTCCCCACCCCTGCATAAGGCAGTTGTTGGTTTTCTTCCCCAATTCTTTTCCAAGTAG
GTTTTGTTTACCCTACTCCCCAAATCCCTGAGCCAGAAAGTGGGGTGCTTATACTCCCAAACCTTGAGTGTCCAGC
CTTCCCCCTGTTGTTTTTGTCTCTTGTGCTGTGCCTAGTGGCACCTGGGCTGGGGAGGACACTGCCCGTCTAGG
TTTTTATAAATGTCTTACTCAAGTTCAAACCTCCAGCCTGTGAATCAACTGTGTCTCTTTTTTTGACTTGGTAAGC
AAGTATTAGGCTTTGGGGTGGGGGAGGTCTGTAATGTGAAACAACCTTCTGTCTTTTTTTCTCCCACTGTTGTA
AATAACTTTTAATGGCCAAACCCAGATTTGTACTTTTTTTTTTTCTAACTGCTAAAACCATTTCTCTCCACCT
GGTTTTACTGTAAACATTTGGAAAAGGAATAAATGTCGTCCCTTTTTAAAAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 83

MGSQSSKAPRGDVTAEAAAGASPAKANGQENGHVKSNGDLSPKGEGESPPVNGTDEAAGATGDAIEPAPPSQGAE
AKGEVPPKETPKKKKKFSFKKPKLSGLSFKRNRKEGGDSSASSPTEEEQEQQEIGACSDGTAQEGKAAATPE
SQEPQAKGAEASAASEEEEAGPQATEPSTPSGPESGPTPASAEQNE

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FIGURE 84

GCGGAGCGTGTGAGCAGTACTGCGGCCTCCTCTCCTCTCCTAACCTCGCTCTCGCGGCCTACCTTTACCCGCCCG
CCTGCTCGGCGACCAGCGGGGATCCTCCCCCAGCCGCAAGTCCACGAAGAAAGCAACGAATGAAAATTATGAAGA
CAACGAGAAGTCAGACTCCTCCGGGTCGCGCTCCAGCTGCTTCGGCTTCGTCGCCTACTCTGTGAAGTCCGGGGA
GAGATCTCGAGTCAAGATTAAGACCTTAACCCACCAACCTGCCTGTTTCGGACACCCCCCGGGCCGGCCGCTGTCT
GTCCCTTTCTCCATCGCCCTCTCCCAGAAAGCTCCGGTGCTTGGACCAGCTAGAGTCTGAGAAAGAGGAGAGGCG
CGAACGCCACTCCAAAAAGAGAAGGGTTAAAGAGGGCAACCCTAACGATACGCTTGACTTTCTGTGGCTGGGAAC
ACCTTCCACC**ATGA**ACCACCTCAGCAAGTTCCTCACTTAAATAAAGGCATCAAGCAGGTGTACATGTCCCTGCCTCA
GGGTGAGAAAGTCCAGGCCATGTATATCTGGATCGATGGTACTGGAGAAGGACTGCGCTGCAAGACCCGGACCCT
GGACAGTGAGCCCAAGTGTGTGGAAGAGTTGCCTGAGTGGAATTTTCGATGGCTCCAGTACTTTACAGTCTGAGGG
TTCCAACAGTGACATGTATCTCGTGCCTGCTGCCATGTTTCGGGACCCCTTCCGTAAGGACCCTAACAAAGCTGGT
GTTATGTGAAGTTTTCAAGTACAATCGAAGGCCTGCAGAGACCAATTTGAGGCACACCTGTAAACGGATAATGGA
CATGGTGAGCAACCAGCACCCCTGGTTTGGCATGGAGCAGGAGTATACCCTCATGGGGACAGATGGGCACCCCTT
TGGTTGGCCTTCCAACGGCTTCCCAGGGCCCCAGGGTCCATATTACTGTGGTGTGGGAGCAGACAGAGCCTATGG
CAGGGACATCGTGGAGGCCATTACCGGGCCTGCTTGTATGCTGGAGTCAAGATTGCGGGGACTAATGCCGAGGT
CATGCCTGCCAGTGGGAATTTTCAGATTGGACCTTGTGAAGGAATCAGCATGGGAGATCATCTCTGGGTGGCCCCG
TTTCATCTTGCATCGTGTGTGTGAAGACTTTGGAGTGATAGCAACCTTTGATCCTAAGCCCATTCCTGGGAAGTG
GAATGGTGCAGGCTGCCATACCAACTTCAGCACCAAGGCCATGCGGGAGGAGAATGGTCTGAAGTACATCGAGGA
GGCCATTGAGAACTAAGCAAGCGGCACCAGTACCACATCCGTGCCTATGATCCCAAGGGAGGCCTGGACAATGC
CCGACGTCTAACTGGATTCCATGAAACCTCCAACATCAACGACTTTTCTGCTGGTGTAGCCAATCGTAGCGCCAG
CATACGCATTCCCCGGACTGTTGGCCAGGAGAAGAAGGGTTACTTTGAAGATCGTCGCCCTCTGCCAACTGCGA
CCCCTTTTCGGTGACAGAAGCCCTCATCCGCACGTGTCTTCTCAATGAAACCGGCGATGAGCCCTTCCAGTACAA
AAATT**TAA**TGGACTAGACCTCCAGCTGTTGAGCCCTCCTAGTTCTTCATCCCACTCCAACCTCTTCCCCCTCTCC
CAGTTGTCCCGATTGTAACCTCAAAGGTGGAATATCAAGGTCGTTTTTTTCATTCCATGTGCCAGTTAATCTTG
CTTTCTTTGTTTGGCTGGGATAGAGGGTCAAGTTATTAATTTCTTCACACCTACCCTCCTTTTTTTTCCCTATCA
CTGAAGCTTTTTAGTGCATTAGTGGGAGGAGGGTGGGGAGACATAACCACTGCTTCCATTTAATGGGGTGCACC
TGTCCAATAGGCGTAGCTATCCGGACAGAGCACGTTTGCAGAAGGGGGACTCTTCTTCCAGGTAGCTGAAAGGGG
AAGACCTGACGTACTCTGGTTAGGTTAGGACTTGCCCTCGTGGTGGAACCTTTTCTTAAAAAGTTATAACCAACT
TTTCTATTAAAAAGTGGGAATTAGGAGAGAAGGTAGGGGTGGGAATCAGAGAGAATGGCTTTGGTCTCTTGCTTG
TGGGACTAGCCTGGCTTGGGACTAAATGCCCTGCTCTGAACACGAAGCTTAGTATAAACTGATGGATATCCCTAC
CTTGAAAGAAGAAAAGGTTCTTACTGCTTGGTCTTGATTTATCACACAAAGCAGAATAGTATTTTTATATTTAA
ATGTAAAGACAAAAAACTATATGTATGGTTTTGTGGATTATGTGTGTTTTGCTAAAGGAAAAAAACCATCCAGGTC
ACGGGGCACCAAATTTGAGACAAATAGTCGGATTAGAAATAAAGCATCTCATTTTGAGTAGAGAGCAAGGGAAGT
GGTTCTTAGATGGTGATCTGGGATTAGGCCCTCAAGACCCCTTTGGGTTTCTGCCCTGCCACCCTCTGGAGAAG
GTGGGCACTGGATTAGTTAACAGACGACACGTTACTAGCAGTCACTTGATCTCCGTGGCTTTGGTTTAAAAGACA
CACTTGTCCACATAGGTTTAGAGATAAGAGTTGGCTGTTCAACTTGAGCATGTTACTGACAGAGGGGGTATTGGG
GTTATTTTCTGGTAGGAATAGCATGTCACTAAAGCAGGCCTTTTGATATTAAATTTTTTAAAAAGCAAAATTATA
GAAGTTTAGATTTTAAATCAAAATTTGTAGGGTTTTCTAGGTAATTTTTTACAGAATTGCTTGTTTGCTTCAACTGTCT
CCTACCTCTGCTCTTGGAGGAGATGGGGACAGGGCTGGAGTCAAAACACTTGTAATTTTGTATCTTGATGTCTTT
GTTAAGACTGCTGAAGAATTATTTTTTTTTCTTTTATAATAAGGAATAAACCCACCTTTATTCTTTCATTTTCATC
TACCATTTTCTGGTCTTGTGTTGGCTGTGGCAGGCCAGCTGTGGTTTTCTTTTGCCATGACAACCTTCTAATTGC
CATGTACAGTATGTTCAAAGTCAAATAACTCCTCATTGTAAACAACTGTGTAAGTGGCCAAAGCAGCACTTATA
AATCAGCCTAACATAA

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FIGURE 85

MTTSASSHLNKGIKQVYMSLPQGEKVQAMYIWIDGTGEGLRCKTRTLDSEPKCVEELPEWNFDGSSTLQSEGSNS
DMYLVPAAMFRDPFRKDPNKLVLCEVFKYNRRPAETNLRHTCKRIMDMVSNQHPWFGMEQEYTLMGTDGHPFGWP
SNGFPGPQGPIYCGVGADRAYGRDIVEAHYRACLYAGVKIAGTNAEVMFPAQWEFQIGPCEGISMGDHLWVARFIL
HRVCEDFGVIATFDPKPIPGNWNGAGCHTNFSTKAMREENGLKYIEEAIEKLSKRHQYHIRAYDPKGGLDNARRL
TGFHETSNINDFSAGVANRSASIRIPRTVGQEKKG YFEDRRPSANCDPFSVTEALIRTCLLNETGDEPFQYKN

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FIGURE 86

AGTATGTGTGGTTGGGGAATTCATGTGGAGGTCAGAGTGGAAGCAGGTGTGAGAGGGTCCAGCAGAAGGAAACAT
GGCTGCCAAAGTGTGTTGAGTCCATTGGCAAGTTTGGCCTGGCCTTAGCTGTTGCAGGAGGCGTGGTGAACCTCTGC
CTTATATAATGTGGATGCTGGGCACAGAGCTGTCATCTTTGACCGATTCCGTGGAGTGCAGGACATTGTGGTAGG
GGAAGGGACTCATTTTCTCATCCCGTGGGTACAGAAACCAATTATCTTTGACTGCCGTTCTCGACCACGTAATGT
GCCAGTCATCACTGGTAGCAAAGATTTACAGAATGTCAACATCACACTGCGCATCCTCTTCCGGCCTGTCGCCAG
CCAGCTTCCTCGCATCTTCACCAGCATCGGAGAGGACTATGATGAGCGTGTGCTGCCGTCCATCACAACCTGAGAT
CCTCAAGTCAGTGGTGGCTCGCTTTGATGCTGGAGAACTAATCACCAGAGAGAGCTGGTCTCCAGGCAGGTGAG
CGACGACCTTACAGAGCGAGCCGCCACCTTTGGGCTCATCTGGATGACGTGTCCTTGACACATCTGACCTTCGG
GAAGGAGTTCACAGAAGCGGTGGAAGCCAAACAGGTGGCTCAGCAGGAAGCAGAGAGGGCCAGATTTGTGGTGGA
AAAGGCTGAGCAACAGAAAAAGGCGGCCATCATCTCTGCTGAGGGCGACTCCAAGGCAGCTGAGCTGATTGCCAA
CTCACTGGCCACTGCAGGGGATGGCCTGATCGAGCTGCGCAAGCTGGAAGCTGCAGAGGACATCGCGTACCAGCT
CTCACGCTCTCGGAACATCACCTACCTGCCAGCGGGGCGAGTCCGTGCTCCTCCAGCTGCCCCAGTGAGGGGCCAC
CCTGCCTGCACCTCCGCGGGCTGACTGGGCCACAGCCCCGATGATTCTTAACACAGCCTTCCTTCTGCTCCCACC
CCAGAAATCACTGTGAAATTTATGATTGGCTTAAAGTGAAGGAAATAAAGGTAAAATCACTTCAGATCTCTAAT
TAGTCTATCAAAATGAAACTCTTTCACTTCTCTCACATCCATCTACTTTTTTATCCACCTCCCTACCAAAAATTGC
CAAGTGCCTATGCAAACCAGCTTTAGGTCCCAATTCGGGGCCTGCTGGAGTTCCGGCCTGGGCACCAGCATTGG
CAGCACGCAGGCGGGGCAGTATGTGATGGACTGGGGAGCACAGGTGTCTGCCTAGATCCACGTGTGGCCTCCGTC
CTGTCACTGATGGAAGGTTTGC GGATGAGGGCATGTGCGGCTGAACTGAGAAGGCAGGCCTCCGTCTTCCCAGCG
GTTCTCTGTGCAGATGCTGCTGAAGAGAGGTGCCGGGGAGGGGCAGAGAGGAAGTGGTCTGTCTGTTACCATAAGT
CTGATTCTCTTTAACTGTGTGACCAGCGGAAACAGGTGTGTGTGAACTGGGCACAGATTGAAGAATCTGCCCCCTG
TTGAGGTGGGTGGGCCTGACTGTTGCCCCCAGGGTCCTAAACTTGGATGGACTTGTATAGTGAGAGAGGAGGC
CTGGACCGAGATGTGAGTCCTGTTGAAGACTTCCTCTCTACCCCCACCTTGGTCCCTCTCAGATACCCAGTGGA
ATTCCAACCTGAAGGATTGCATCCTGCTGGGGCTGAACATGCCTGCCAAAGACGTGTCCGACCTACGTTCTTGGC
CCCCTCGTTCAAGAGACTGCCCTTCTCACGGGCTCTATGCCTGCACTGGGAAGGAAACAAATGTGTATAAACTGCT
GTCAATAAAATGACACCCAGACCTTCC

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FIGURE 87

MAAKVFESIGKFGLALAVAGGVVNSALYNVDAGHRAVIFDRFRGVQDIVVGEGTHFLIPWVQKPIIFDCRSRPRN
VPVITGSKDLQNVNITLRILFRPVASQLPRIFTSIGEDYDERVLPSITTEILKSVMVARFDAGELITQRELVSRQV
SDDLTERAATFGLILDDVSLTHLTFGKEFTEAVEAKQVAQQEAERARFVVEKAEQQKKAIIISAEGDSKAAELIA
NSLATAGDGLIELRKLEAAEDIAYQLSRSRNITYLPAGQSVLLQLPQ

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FIGURE 88

GGCACGAGGGGCCGGGGGGCGCAGCTAGAGAGCCCCGGAGCCGCGCGGGAGAGGAACGCGCAGCCAGCCTTGGG
AAGCCCAGGCCCCGGCAGCCATGGCGGTGGAAGGAGGAATGAAATGTGTGAAGTTCTTGCTCTACGTCCCTCCTGCT
GGCCTTTTGGCCTGTGCAGTGGGACTGATTGCCGTGGGTGTCGGGGCACAGCTTGTCTGAGTCAGACCATAAT
CCAGGGGGCTACCCCTGGCTCTCTGTTGCCAGTGGTCATCATCGCAGTGGGTGTCTTCCTCTTCCTGGTGGCTTT
TGTGGGCTGCTGCGGGGCCCTGCAAGGAGAACTATTGTCTTATGATCACGTTTGCCATCTTTCTGTCTCTTATCAT
GTTGGTGGAGGTGGCCGCAGCCATTGCTGGCTATGTGTTTAGAGATAAGGTGATGTCAGAGTTTAATAACAACCTT
CCGGCAGCAGATGGAGAATTACCCGAAAAACAACCACACTGCTTCGATCCTGGACAGGATGCAGGCAGATTTTAA
GTGCTGTGGGGCTGCTAACTACACAGATTGGGAGAAAATCCCTTCCATGTCGAAGAACCGAGTCCCCGACTCCTG
CTGCATTAATGTTACTGTGGGCTGTGGGATTAATTTCAACGAGAAGGCGATCCATAAGGAGGGCTGTGTGGAGAA
GATTGGGGGCTGGCTGAGGAAAAATGTGCTGGTGGTAGCTGCAGCAGCCCTTGGAATTGCTTTTGTGAGGTTTT
GGGAATTGTCTTTGCCTGCTGCCTCGTGAAGAGTATCAGAAGTGGCTACGAGGTGATGTAGGGGTCTGGTCTCCT
CAGCCTCCTCATCTGGGGGAGTGGAATAGTATCCTCCAGGTTTTTCAATTAAACGGATTATTTTTTTCAGACCGAA
AAGAAAAAAAAAAAAAAAAAAAAA

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FIGURE 89

MAVEGGMKCVKFLLYVLLLAFCACAVGLIAVGVGAGLVLSQTIIQGATPGSLLPVVIIAVGVFLFLVAFVGCCGA
CKENYCLMITFAIFLSLIMLVEVAAAIAGYVFRDKVMSEFNNNFRQQMENYPKNNHTASILDRMQADFKCCGAAN
YTDWEKIPSMKSNRVPDSCCINVTVGCGINFNEKAHKEGCVKEKIGWLRKNVLVAAAAALGIAFVEVLGIVFAC
CLVKSIRSGYEVN

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FIGURE 90

CGGGAGAGCGCGCTCTGCCTGCCGCCTGCCTGCCACTGAGGGTTCCCAGCACCAATGAGGGCCTGGATCTTC
TTTCTCCTTTGCCTGGCCGGGAGGGCCTTGGCAGCCCCCTCAGCAAGAAGCCCTGCCTGATGAGACAGAGGTGGTG
GAAGAAACTGTGGCAGAGGTGACTGAGGTATCTGTGGGAGCTAATCCTGTCCAGGTGGAAGTAGGAGAATTTGAT
GATGGTGCAGAGGAAACCGAAGAGGAGGTGGTGGCGGAAAATCCCTGCCAGAACCACCACTGCAAACACGGCAAAG
GTGTGCGAGCTGGATGAGAACAACACCCCCATGTGCGTGTGCCAGGACCCACCAGCTGCCCAGCCCCCATTTGGC
GAGTTTGAGAAGGTGTGCAGCAATGACAACAAGACCTTCGACTCTTCCTGCCACTTCTTTGCCACAAAGTGCACC
CTGGAGGGCACCAAGAAGGGCCACAAGCTCCACCTGGACTACATCGGGCCTTGCAAATACATCCCCCCTTGCCTG
GACTCTGAGCTGACCGAATTCCCCCTGCGCATGCGGGACTGGCTCAAGAACGTCCTGGTCACCCTGTATGAGAGG
GATGAGGACAACAACCTTCTGACTGAGAAGCAGAAGCTGCGGGTGAAGAAGATCCATGAGAATGAGAAGCGCCTG
GAGGCAGGAGACCACCCCGTGGAGCTGCTGGCCCGGGACTTCGAGAAGAATAACATGTACATCTTCCCTGTA
CACTGGCAGTTTCGGCCAGCTGGACCAGCACCCCATTTGACGGGTACCTCTCCCACACCGAGCTGGCTCCACTGCGT
GCTCCCCCTCATCCCCATGGAGCATTGCACCACCCGCTTTTTTCGAGACCTGTGACCTGGACAATGACAAGTACATC
GCCCTGGATGAGTGGGCCGGCTGCTTCGGCATCAAGCAGAAGGATATCGACAAGGATCTTGTGATCTTAAATCCAC
TCCTTCCACAGTACCGGATTCTCTCTTTAACCTCCCCTTCGTGTTTCCCCCAATGTTTAAAATGTTTGGATGGT
TTGTTGTTCTGCCTGGAGACAAGGTGCTAACATAGATTTAAGTGAATACATTAACGGTGCTAAAAATGAAAATTC
TAACCCAAGACATGACATTCTTAGCTGTAACCTAACTATTAAGGCCTTTTCCACACGCATTAATAGTCCCATTTT
TCTCTTGCCATTTGTAGCTTTGCCCATTTGTCTTATTGGCACATGGGTGGACACGGATCTGCTGGGCTCTGCCTTA
AACACACATTGCAGCTTCAACTTTTCTCTTTAGTGTCTGTTTGAACTAATACTTACCGAGTCAGACTTTGTGT
TCATTTTCATTTCAGGGTCTTGGCTGCCTGTGGGCTTCCCCAGGTGGCCTGGAGGTGGGCAAAGGGAAAGTAACAGA
CACACGATGTTGTCAAGGATGGTTTTTGGGACTAGAGGCTCAGTGGTGGGAGAGATCCCTGCAGAATCCACCAACC
AGAACGTGGTTTGCCTGAGGCTGTAACCTGAGAGAAAAGATTCTGGGGCTGTCTTATGAAAATATAGACATTCTCAC
ATAAGCCCAGTTTCATCACCATTTTCTCCTTTTACCTTTTCAGTGCAGTTTCTTTTTCACATTAGGCTGTTGGTTCAAA
CTTTTGGGAGCACGGACTGTGAGTTCTCTGGGAAGTGGTCAGCGCATCCTGCAGGGCTTCTCCTCCTCTGCTTTT
TGGAGAACCAGGGCTCTTCTCAGGGGCTCTAGGGACTGCCAGGCTGTTTCAGCCAGGAAGGCCAAAATCAAGAGT
GAGATGTAGAAAGTTGTAAATAGAAAAAGTGGAGTTGGTGAATCGGTTGTTCTTTCTCACATTTGGATGATTG
TCATAAGGTTTTTAGCATGTTCTCCTTTTCTTCACCCTCCCCTTTGTTCTTCTATTAATCAAGAGAACTTCAA
AGTTAATGGGATGGTCGGATCTCACAGGCTGAGAACTCGTTCACCTCCAAGCATTTTCATGAAAAAGCTGCTTCTT
ATTAATCATACAACTCTCACCATGATGTGAAGAGTTTCACAAATCTTTCAAATAAAAAGTAATGACTTAGAAA
CTGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 91

MRAWIFFLLCLAGRALAAPQQEALPDETEVVEETVAEVTEVSVGANPVQVEVGEFDDGAEETEEVVVAENPCQNH
HCKHGKVCELDENNTPMCVCQDPTSCPAPIGEFEKVCSNDNKTFDSSCHFFATKCTLEGTKKGHKLHLDYIGPCK
YIPPCLDSELTEFPLMRDWLKNVLVTLYERDEDNNLLTEKQKLRVKKIHENEKRLEAGDHPVELLARDFEKNYN
MYIFPVHWQFGQLDQHPIDGYLSHTELAPLRAPLIPMEHCTTRFFETCDLDNDKYIALDEWAGCFGIKQKDIDKD
LVI

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FIGURE 92

CCGGCCCGCGCCCCGCAGGCCGCCCGCCCGCCCGCGCCGCCATGGGAGTGGAGGGCTGCACCAAGTGCAATCAAGTA
CCTGCTCTTCGTCTTCAATTTTCGTCTTCTGGCTGGCTGGAGGCGTGATCCTGGGTGTGGCCCTGTGGCTCCGCCA
TGACCCGCAGACCACCAACCTCCTGTATCTGGAGCTGGGAGACAAGCCCGCGCCCAACACCTTCTATGTAGGCAT
CTACATCCTCATCGCTGTGGGCGCTGTCATGATGTTTCGTTGGCTTCCTGGGCTGCTACGGGGCCATCCAGGAATC
CCAGTGCCCTGCTGGGGACGTTCTTCACCTGCCTGGTCATCCTGTTTGCCTGTGAGGTGGCCGCCGGCATCTGGGG
CTTTGTCAACAAGGACCAGATCGCCAAGGATGTGAAGCAGTTCTATGACCAGGCCCTACAGCAGGCCGTGGTGA
TGATGACGCCAACAACGCCAAGGCTGTGGTGAAGACCTTCCACGAGACGCTTGACTGCTGTGGCTCCAGCACACT
GACTGCTTTGACCACCTCAGTGCTCAAGAACAATTTGTGTCCCTCGGGCAGCAACATCATCAGCAACCTCTTCAA
GGAGGACTGCCACCAGAAGATCGATGACCTCTTCTCCGGGAAGCTGTACCTCATCGGCATTGCTGCCATCGTGGT
CGCTGTGATCATGATCTTCGAGATGATCCTGAGCATGGTGCTGTGCTGTGGCATCCGGAACAGCTCCGTGTACTG
AGGCCCCGCAGCTCTGGCCACAGGGACCTCTGCAGTGCCCCCTAAGTGACCCGGACACTTCCGAGGGGGCCATCA
CCGCCTGTGTATATAACGTTTCCGGTATTACTCTGCTACACGTAGCCTTTTTACTTTTGGGGTTTTGTTTTTGT
CTGAACTTTCCTGTTACCTTTTCAGGGCTGACGTCACATGTAGGTGGCGTGTATGAGTGGAGACGGGCCTGGGTC
TTGGGGACTGGAGGGCAGGGGTCCTTCTGCCCTGGGGTCCCAGGGTGCTCTGCCTGCTCAGCCAGGCCTCTCCTG
GGAGCCACTCGCCAGAGACTCAGCTTGGCCAACTTGGGGGGCTGTGTCCACCCAGCCCGCCCGTCCTGTGGGCT
GCACAGCTCACCTTGTTCCCTCCTGCCCCGGTTCGAGAGCCGAGTCTGTGGGCACTCTCTGCCTTCATGCACCTG
TCCTTTCTAACACGTCGCCTTCAACTGTAATCACAAACATCCTGACTCCGTCATTTAATAAAGAAGGAACATCAGG
CATGCTAAA

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FIGURE 93

MGVEGCTKCIKYLLFVFNFVFWLAGGVILGVALWLRHDPQTTNLLYLELGDKPAPNTFYVGIYILIAVGAVMMFV
GFLGCGYGAIQESQCLLGTTFTCLVILFACEVAAGIWGFVNKDQIAKDVKQFYDQALQQAVVDDDANNAKAVVKTF
HETLDCCGSSTLTALTTSVLKNNLCPSGSNIISNLFKEDCHQKIDDLFSGKLYLIGIAAIVVAVIMIFEMILSMV
LCCGIRNSSVY

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FIGURE 94A

GCTAAGTTAGCTTTTCAACTGGCACTGTATGGCAGCATTTTTGGTATGGTTAGCGTGGCACATGGCGAAACATAA
AGCATTTTACTGTACAGGTAAGGAATGTGCCATGTGTTTTACCTATCTCTCTTTCTCTCTCACTCCCATGCACAC
ATCCTGTGTGTATTTCAGAGACCTTCAGAAACATTCATATTCATTTTCATGAGTCAGCAAAGCCCTATGCTTGAT
TCCAACAGAATATTTCCCTTTACATACTTTCTTCTCTTAATTTTTACAAAATTGTATGGTAGGTGTAAAAGAAAAT
CATAGTAACTGTACCATATTATTAACCCCTAAATCAAACTTTTTTTTGTCTTGTGTATCTTGATTTTTCTGTGTGC
TTTATAGTGAAGCAGCCGACACGAGTCGTTGTTTATAAAACAGCTTTTGAAAGTTGAGAGCACACCCCTGGAGAA
CCGACTGTGCTTGCTTACGTTTGGTTCATGACTTAAAAATCGAGTACAGGTGATGAAATCTTGCGAGTGTTAACA
AAAAAGTAGTGTGTATTGTGCTATTTTTTTTTTACTCTAGAACTTAACCATTGTAGAGAAAAAGGAAACAAAT
TTTCACACATTGAAGTTCATTCTGACATAAAATTAATGATAAATAATCATAGAAATCAAGCTTTGTATTTTAGCG
AACATAAGTACTTTCAACAACTCAGGTGGTGTATCAGGGAGACATTTTCTGGGTGTTTTTGTGTGTTTTCTGTCTC
TTAGAAAAGAATGTGTTCTAATGCAAGGATGTTTTCTCTGCAGGAGTTATTCCTGATGAAGCTAAAGCTTTGTCTC
TGTTGGCACCAGCTAATGCAGTGGCAGGTCTTCTGCCTGGTGGTGGACTCCTGCCTACTCCTAACCCACTTACCC
AGATTGGCGCTGTTCCACTGGCTGCTTTGGGGGCTCCTACTCTTGATCCTGCCCTTGCTGCACCTGGGCTTCCTG
GAGCAAACCTGAACTCTCAGTCTCTTGCTGCAGATCAGTTGCTGAAGCTTATGAGTACTGTTGATCCCAAGTTGA
ATCATGTAGCTGCTGGTCTCGTTTACCAAGTCTGAAATCGGATACCTCTAGTAAAGAAATAGAGGAAGCTATGA
AAAGAGTACGAGAAGCACAGTCCCTAATTTCTGCTGCTATAGAACCAGATAAGAAAGAAGAAAAAGAAGGCATT
CAAGATCAAGATCACGTTCTAGGAGGAGGAGGACTCCCTCATCTTCTAGACACAGGCGGTCAAGAAGCAGATCGA
GACGGCGGTACATTTCTAAGTCTAGGAGTCGGCGACGATCCAAAAGCCCAAGGCGGAGAAGATCTCATTCCAGAG
AAAGAGGTAGAAGGTCAAGGAGCACATCAAAAACAAGAGACAAAAGAAAGACAAAGAAAAGAAACGTTCTA
AAACACCACCAAAAAGTTACAGCACAGCCAGACGTTCTAGAAGTGCAAGCAGAGTATATTTGAAGTAACATGGAA
TTCAAGAGAGAGAGAGACGACGACGAAGAAGCAGGAGTGGCACAAGATCTCCTAAAAGCCTCGGTCTCCTAAAA
GAAAATTGTCCCGCTCACCATCCCTAGGAGACATAAAAAGGAGAAGAAGAAAGATAAAGACAAAGAAAGAAGTA
GGGATGAAAGAGAACGATCAACAAGCAAGAAGAAGAGATAAGGAAAAGGACCGGGAAGAAAATCAG
AGAGTGATAAAGATGTAAACAGGTTACACGGGATTATGATGAAGAGGAACAGGGGTATGACAGTGAGAAAGAGA
AAAAAGAAGAGAAGAAACCAATAGAAACAGGTTCCCTAAAACAAAGGAATGTTCTGTGGAAGGGAAGGAACTGGTG
ATTCATAAGAGAATCCAAAGTGAATGGGGATGATCATCATGAAGAAGACATGGATATGAGTGACTGAATATTGC
CTCTGAGGGAGTCCAACGTGTATACCTGCATCAGTGTCAATTCCTTTGTGTGATTCTTAATGCTGTATTTGTTTCAT
CTCAAACCTAGATGTATACAGCTCTGAGTTATAAATGGTTATAAAGCTCCTGTTACTCATATTAGTTATTTACAT
CAAAAAGCTTTTAGAAAATGGTACGAGGTAACCAATTCCTGTGCATGGTGAAATCTGATTGAGTAACCAAGCAGTT
TTACTATTCTGGTGCTGCTTCATAACAAAATGAAAAGCTGCATGCATCTACAGCAGGCATGGATTGTTTATGTC
GTATGATATCCTTTATTAAGTAAGTTCACTTATAGTATTTCTATAATTTGATTCAATGCGTAATAGAGCCATGT
AGGAAATGCACTGATTGCATGTTATTGTGGCAAGAATATCCTAAATGTCATTAATAATCCTCCAACATGATGGATC
TACTTATGGTCTTGTGTTGACATGACAAATTAACATTCCTTATAGTTACATCTGGAATGAGCATTGAAATAG
ATAATCCTTTAAGCCTTGTGGCAAAATTTTTGTGGCTTTTGTTTAACTTTGAAAGGTTATTATGCACTAACCTTT
TTTGGTGGCTAATTAGGGTTTAAATACAGAAACAAGATTTCAAATAAACTGTCTTTGGCAGTGAGTAAATAGCA
TATTTTGAAGTAGAGTTGTATACTTTTTTACATAAGATGTTTGGGAATTTTTTCTGAAGTAATAATTTATTCCAC
ATCTACATCAGTGAAAGCTATCTACCTATCCTGAGTCTATCTTAAAGGAAAAAAGAAAAAACCTTATCTCTTG
CCCTTATTTTGAATTTTCCACTCTTTTCAATTAATTTGTTTTAAGCTCCGTGTTGGAAAAAAGGGGTAGTGCATTTT
AAATTGACCTTCATACGCTTTTAAATAAGACAAATCTACTTGATAATGTACCTTTATTTGATCTCAAGTTGTAT
AAAACCAATAAATTTGTGTTACTGCAGTAGTAATCTTATGCACACGGTGATTTCAITGTTATATATGCAAAGTAGG
CAACTGTTTTCTTAGTTACAGAAGTTTCAAGCTTCACTTTTGTGCAGTAGAAACAAAAGTAGGCTACAGTCTGTG
CCATGTTGATGTACAGTTTCTGAAATTGTTTTACAAGACTTTGATAATAAAACCCTTAAACTTATGTTTCATGTTT
CTGTAAACCGTATTTGTATTTATTTACGCTACTGAATGTATGACATTTACCTCATTCAATTTACAAATTCCTTC
CCTTTCTGTCCACATATTTAGTATAGTAAAAAGAGGAAGTCTATCACTGTAGTGATAATTGCCATCAAAATTTGT
CAAAAATGATTTAATTTCTATCCAAATAGTCCTTTTCTTAGCTTAGTATCATTTTATTGCTTATTTTTTGTGTG
GGAATGGGGTTGGATAAAGCAATGAACTTTAGTATAAACAAATCCCACCTATATCTAGCAAATTTATATTTTCGG
TGAAATACAGATATTTGCCTTTCTGGAGTAGTATAGAAGCTGTCAATATGTATCTACTGTACAGTACTAAATAGT
ATTCATTTATGAAATGAGTAGTGTGTTGGGTGGCTGGGGTTAAGGGAAAATGAGACTTGAATGTAGCTTTTATC

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FIGURE 94B

CAAGTTTTGAGTATAAATAGGGTTTTGTTTTGTTTTTTTTTAACCTAAAAACTGAAATGCCATATAGAAAAACAGC
ATTGTTTTTACAGTTTGTAGTAAGTAACTTTTTAAAGATTTTATCAAAAAGAATTTTGTCTATAGTGAGTAAAAG
AAGTTCTAATAATGGTCCTAATCACTGCATTTTTAAAAAACAAAGTCAACACAAATGACATTTGTTTTAACTT
TAGTAGATAAAAAGGTGAACCATGTGACATGGGCATTTTTGTAAGTCAAAAACAAATTTACATATGGTAAACCTA
ATATTCACAGTGTTTCCCTCACTTGTAATCTCTGAATACAAATATACTAGCTTTTCTAAAGGGAATCATTTTTT
TAAAAGTAGTGCCACTGACAAGATGCTACAGTGAAGATTATCCATTCTTAGGATATTTATTTTCAGTGAACATTT
TCTGCACAAAGGTAGTGTGCACTGGGACACAAGCCTTTTAACAGATAACCAGTTGAAATCAAACACTGCCTCCA
CACCGAGTTCTGTTGTGTATTTGATAGTAAATTGATTTAAAAATAAAAGTGGTTTTTGTTAGAAA

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FIGURE 96

GGCACGAGGGGAGCGCTTGTTTGCTGCCTCGTACTCCTCCATTTATCCGCCATGATAAGTGCCAGCCGAGCTGCA
GCAGCCCGTCTCTCGTGGGCGCCGCAGCCTCCCGGGGCCCTACGGCCGCCGCCACCAGGATAGCTGGAATGGCCTT
AGTCATGAGGCTTTTAGACTTGTTTCAAGGCGGGATTATGCATCAGAAGCAATCAAGGGAGCAGTTGTTGGTATT
GATTTGGGTACTACCAACTCCTGCGTGGCAGTTATGGAAGGTAAACGAGCAAAGGTGCTGGAGAATGCCGAAGGT
GCCAGAACCACCCCTTCAGTTGTGGCCTTTACAGCAGATGGTGAGCGACTTGTTGGAATGCCGGCCAAGCGACAG
GCTGTCACCAACCCAAACAATACATTTTATGCTACCAAGCGTCTCATTGGCCGGCGATATGATGATCCTGAAGTA
CAGAAAGACATTAAAAATGTTCCCTTTAAATTTGTCCGTGCCTCCAATGGTGATGCCTGGGTTGAGGCTCATGGG
AAATTGTATTCTCCGAGTCAGATTGGAGCATTTGTGTTGATGAAGATGAAAGAGACTGCAGAAAATTACTTGGGG
CGCACAGCAAAAAATGCTGTGATCACAGTCCAGCTTATTTCAATGACTCGCAGAGACAGGCCACTAAAGATGCT
GGCCAGATATCTGGACTGAATGTGCTTCGGGTGATTAATGAGCCACAGCTGCTGCTCTTGCTATGGTCTAGAC
AAATCAGAAGACAAAGTCATTGCTGTATATGATTTAGGTGGTGGAACCTTTGATATTTCTATCCTGGAAATTCAG
AAAGGAGTATTTGAGGTGAAATCCACAAATGGGGATACCTTCTTAGGTGGGAAGACTTTGACCAGGCCTTGCTA
CGGCACATTGTGAAGGAGTTCAAGAGAGAGACAGGGGTTGATTTGACTAAAGACAACATGGCACTTCAGAGGGTA
CGGGAAGCTGCTGAAAAGGCTAAGTGTGAACCTCTCCTCATCTGTGCAGACTGACATCAATTTGCCCTATCTTACA
ATGGATTCTTCTGGACCCAAGCATTTGAATATGAAGTTGACCCGTGCTCAATTTGAAGGGATTGTCACTGATCTA
ATCAGAAGGACTATCGCTCCATGCCAAAAAGCTATGCAAGATGCAGAAGTCAGCAAGAGTGACATAGGAGAAAGTG
ATTCTTGTTGGGTGGCATGACTAGGATGCCCAAGGTTTCAGCAGACTGTACAGGATCTTTTTTGGCAGAGCCCCAAGT
AAAGCTGTCAATCCTGATGAGGCTGTGGCCATTGGAGCTGCCATTGAGGGAGGTGTGTTGGCCGGCGATGTCACG
GATGTGCTGCTCCTTGATGTCACTCCCCTGTCTCTGGGTATTGAAACTCTAGGAGGTGTCTTTACCAAACTTATT
AATAGGAATACCCTATTCCAACCAAGAAGAGCCAGGTATTCTCTACTGCCGCTGATGGTCAAACGCAAGTGGA
ATTAAGTGTGTCAGGGTGAAAGAGAGATGGCTGGAGACAACAACTCCTTGGACAGTTTACTTTGATTGGAATT
CCACCAGCCCTCTGTTGAGTTCTCAGATTGAAGTTACATTTGACATTGATGCCAATGGGATAGTACATGTTTCT
GCTAAAGATAAAGGCACAGGACGTGAGCAGCAGATTGTAATCCAGTCTTCTGGTGGATTAAGCAAAGATGATATT
GAAAAATATGGTTAAAAATGCAGAGAAATATGCTGAAGAAGACCGGCGAAAGAAGGAACGAGTTGAAGCAGTTAAT
ATGGCTGAAGGAATCATTACGACACAGAAACCAAGATGGAAGAATTCAAGGACCAATTACCTGCTGATGAGTGC
AACAAGCTGAAAGAAGAGATTTCCAAAATGAGGGAGCTCCTGGCTAGAAAAGACAGCGAAACAGGAGAAAAATATT
AGACAGGCAGCATCCTCTCTTCAGCAGGCATCATTGAAGCTGTTTCGAAATGGCATACAAAAAGATGGCATCTGAG
CGAGAAGGCTCTGGAAGTTCTGGCACTGGGGAACAAAAGGAAGATCAAAAGGAGGAAAAACAGTAAATATAGCAG
AAATTTTGAAGCCAGAAGGACAACATATGAAGCTTAGGAGTGAAGAGACTTCCTGAGCAGAAATGGGCGAACTTC
AGTCTTTTTACTGTGTTTTTGCAGTATTCTATATATAATTTCCCTTAATTTGTAAATTTAGTGACCATTAGCTAGT
GATCATTTAATGGACAGTGATTCTAACAGTATAAAGTTTCAATATTCTATGTCCCTAGCCTGTCAATTTTTCAGC
TGCATGTAAAAGGAGGTAGGATGAATTGATCATTATAAAGATTTAACTATTTTATGCTGAAGTGACCATATTTTC
AAGGGGTGAAACCATCTCGCACACAGCAATGAAGGTAGTCATCCATAGACTTGAAATGAGACCACATATGGGGAT
GAGATCCTTCTAGTTAGCCTAGTACTGCTGTACTGGCCTGTATGTACATGGGGTCCTTCAACTGAGGCCTTGCAA
GTCAAGCTGGCTGTGCCATGTTTGTAGATGGGGCAGAGGAATCTAGAACAATGGGAAACTTAGCTATTTATATTA
GGTACAGCTATTAAAAACAAGGTAGGAATGAGGCTAGACCTTTAACTTCCCTAAGGCATACTTTTCTAGCTACCTT
CTGCCCTGTGCTGGCACCTACATCCTTGATGATTGTCTCTTACCCATTCTGGAATTTTTTTTTTTTTTAAATA
AATACAGAAAGCATCTTGAAAAA

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FIGURE 97

MISASRAAAARLVGAAASRGPTAARHQDSWNGLSHEAFRLVSRRDYASEAIKGAVVGIDLGTTNSCVAVMEGKRA
KVLNAEGARTTPSVVAFTADGERLVGMPAKRQAVTNPNNTFYATKRLIGRRYDDPEVQKDIKNVPFKIVRASNG
DAWVEAHGKLYSPSQIGAFVLMKMKETAENYLGRTAKNAVITVPAYFNDSQRQATKDAGQISGLNVLRVINEPTA
AALAYGLDKSEDKVIAVYDLGGGTFDISILEIQKGVFEVKSTNGDTFLGGEDFDQALLRHIVKEFKRETGVDLTK
DNMALQRVREAAEKAKCELSSSVQTDINLPYLTMDSSGPKHLNMKLTRAQFEGIVTDLIRRTIAPCQKAMQDAEV
SKSDIGEVLVGGMTRMPKVQQTVQDLFGRAPSKAVNPDEAVAIGAAIQGGVLAGDVTDVLLLDVTPLSLGIETL
GGVFTKLINRNTTIPTKKSQVFSTAADGQTQVEIKVCQGEREMAGDNKLLGQFTLIGIPPAPRGVFPQIEVTFDID
ANGIVHVSADKGTGREQQIVIQSSGGLSKDDIENMVKNAEKYAEEDRRKKERVEAVNMAEGIIHDTETKMEEFK
DQLPADECNKLKEEISKMRELLARKDSETGENIRQAASSLQQASLKLFFEMAYKKMASEREGSGSSGTGEQKEDQK
EEKQ

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FIGURE 98

GGCACGAGGGGAGCGCTTGTTTGCTGCCTCGTACTCCTCCATTTATCCGCCATGATAAGTGCCAGCCGAGCTGCA
GCAGCCCGTCTCGTGCGCGCCGCAGCCTCCCGGGGCCCTACGGCCGCCCGCCACCAGGATAGCTGGAATGGCCTT
AGTCATGAGGCTTTTAGACTTGTTTCAAGGCGGGATTATGCATCAGAAGCAATCAAGGGAGCAGTTGTTGGTATT
GATTTGGGTACTACCAACTCCTGCGTGGCAGTTATGGAAGGTAAACGAGCAAAGGTGCTGGAGAATGCCGAAGGT
GCCAGAACCACCCCTTCAGTTGTGGCCTTTACAGCAGATGGTGAGCGACTTGTTGGAATGCCGGCCAAGCGACAG
GCTGTACCAACCCAAACAATACATTTTATGCTACCAAGCGTCTCATTGGCCGGCGATATGATGATCCTGAAGTA
CAGAAAGACATTAAAAATGTTCCCTTTAAATTGTCCGTGCCTCCAATGGTGATGCCTGGGTTGAGGCTCATGGG
AAATTGTATTCTCCGAGTCAGATTGGAGCATTGTGTGATGAAGATGAAAGAGACTGCAGAAAATTACTTGGGG
CGCACAGCAAAAAATGCTGTGATCACAGTCCAGCTTATTTCAATGACTCGCAGAGACAGGCCACTAAAGATGCT
GGCCAGATATCTGGACTGAATGTGCTTCGGGTGATTAATGAGCCACAGCTGCTGCTCTTGCCTATGGTCTAGAC
AAATCAGAAGACAAAGTCATTGCTGTATATGATTTAGGTGGTGAACTTTTGATATTTCTATCCTGGAAATTCAG
AAAGGAGTATTTGAGGTGAAATCCACAAATGGGGATACCTTCTTAGGTGGGGAAGACTTTGACCAGGCCTTGCTA
CGGCACATTGTGAAGGAGTTCAAGAGAGAGACAGGGGTTGATTTGACTAAAGACAACATGGCACTTCAGAGGGTA
CGGGAAGCTGCTGAAAAGGCTAAGTGTGAACCTCTCTCATCTGTGCAGACTGACATCAATTTGCCCTATCTTACA
ATGGATTCTTCTGGACCCAAGCATTTGAATATGAAGTTGACCCGTGCTCAATTTGAAGGGATTGTCACTGATCTA
ATCAGAAGGACTATCGCTCCATGCCAAAAAGCTATGCAAGATGCAGAAGTCAGCAAGAGTGACATAGGAGAAGTG
ATTCTTGTGGGTGGCATGACTAGGATGCCCAAGGTTTACAGCAGACTGTACAGGATCTTTTTGGCAGAGCCCCAAGT
AAAGCTGTCAATCCTGATGAGGCTGTGGCCATTGGAGCTGCCATTCAGGGAGGTGTGTTGGCCGGCGATGTCACG
GATGTGCTGCTCCTTGATGTCACTCCCCTGTCTCTGGGTATTGAAACTCTAGGAGGTGTCTTTACCAAACCTTATT
AATAGGAATACCCTATTCCAACCAAGAAGAGCCAGGTATTCTCTACTGCCGCTGATGGTCAAACGCAAGTGGA
ATTAAGTGTGTCAGGTTGAAAGAGAGATGGCTGGAGACAACAACTCCTTGGACAGTTTACTTTGATTGGAATT
CCACCAGCCCCCTCGTGGAGTTCCTCAGATTGAAGTTACATTTGACATTGATGCCAATGGGATAGTACATGTTTCT
GCTAAAGATAAAGGCACAGGACGTGAGCAGCAGATTGTAATCCAGTCTTCTGGTGGATTAAGCAAAGATGATATT
GAAAATATGGTTAAAAATGCAGAGAAATATGCTGAAGAAGACCGGCGAAAGAAGGAACGAGTTGAAGCAGTTAAT
ATGGCTGAAGGAATCATTACGACACAGAAACCAAGATGGAAGAATTCAAGGACCAATTACCTGCTGATGAGTGC
AACAAGCTGAAAGAAGAGATTTCCAAAATGAGGGAGCTCCTGGCTAGAAAAGACAGCGAAACAGGAGAAAAATATT
AGACAGGCAGCATCCTCTCTTCAGCAGGCATCATTGAAGCTGTTGAAATGGCATACAAAAAGATGGCATCTGAG
CGAGAAGGCTCTGGAAGTTCTGGCACTGGGGAACAAAAGGAAGATCAAAAGGAGGAAAAACAGTAAATAATAGCAG
AAATTTTGAAGCCAGAAGGACAACATATGAAGCTTAGGAGTGAAGAGACTTCCTGAGCAGAAATGGGCGAACTTC
AGTCTTTTTACTGTGTTTTTGCAGTATTCTATATATAATTTCCCTTAATTTGTAAATTTAGTGACCATTAGCTAGT
GATCATTTAATGGACAGTGATTCTAACAGTATAAAGTTTACAATATTCTATGTCCCTAGCCTGTCAATTTTTCAGC
TGCATGTAAAAGGAGGTAGGATGAATTGATCATTATAAAGATTTAACTATTTTATGCTGAAGTGACCATATTTTC
AAGGGGTGAAACCATCTCGCACACAGCAATGAAGGTAGTCATCCATAGACTTGAAATGAGACCACATATGGGGAT
GAGATCCTTCTAGTTAGCCTAGTACTGCTGTACTGGCCTGTATGTACATGGGGTCCTTCAACTGAGGCCTTGCAA
GTCAAGCTGGCTGTGCCATGTTTGTAGATGGGGCAGAGGAATCTAGAACAATGGGAACTTAGCTATTTATATTA
GGTACAGCTATTAAACAAGGTAGGAATGAGGCTAGACCTTTAACTTCCCTAAGGCATACTTTTCTAGCTACCTT
CTGCCCTGTGTCTGGCACCTACATCCTTGATGATTGTCTCTTACCCATTCTGGAATTTTTTTTTTTTTTAAATA
AATACAGAAAGCATCTTGAAAAA

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FIGURE 99

MISASRAAAARLVGAAASRGPTAARHQDSWNGLSHEAFRLVSRRDYASEAIKGAVVGIDLGTTNSCVAVMEGKRA
KVLENAEGARTTPSVVAFTADGERLVGMMPAKRQAVTNPNNTFYATKRLIGRRYDDPEVQKDIKNVPFKIVRASNG
DAWVEAHGKLYSPSQIGAFVLMKMKETAENYLGRTAKNAVITVPAYFNDSQRQATKDAGQISGLNVLRVINEPTA
AALAYGLDKSEDKVIAVYDLGGGTFDISILEIQKGVFEVKSTNGDTFLGGEDFDQALLRHIVKEFKRETGVDLTK
DNMALQVRVREAAEKAKCELSSSVQTDINLPYLTMDSSGPKHLNMKLTRAQFEGIVTDLIRRTIAPCQKAMQDAEV
SKSDIGEVILVGGMTRMPKVQQTVDLFGRAPSKAVNPDEAVAIGAAIQGGVLAGDVTDVLLLDVTPLSLGIETL
GGVFTKLINRNTTIPTKKSQVFSTAADGQTQVEIKVCQGEREMAGDNKLLGQFTLIGIPPAPRGVPQIEVTFDID
ANGIVHVSADKGTGREQQIVIQSSGGLSKDDIENMVKNAEKYAEEDRRKKERVEAVNMAEGIIHDTETKMEEFK
DQLPADECNKLKEEISKMRELLARKDSETGENIRQAASSLQQASLKLFE MAYKKMASEREGSGSSGTGEQKEDQK
EEKQ

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FIGURE 100

GCCGTGTCGCCACCATGGCTCCGCACCGCCCCGCGCCCGCGCTGCTTTGCGCGCTGTCCCTGGCGCTGTGCGCGC
TGTCGCTGCCCCGTCCGCGCGGCCACTGCGTCGCGGGGGCGTCCCAGGCGGGGGCGCCCCAGGGGCGGGTGCCCC
AGGCGCGGGCCCAACAGCATGGTGGTGGAACACCCCGAGTTCTCAAGGCAGGGAAGGAGCCTGGCCTGCAGATCT
GGCGTGTGGAGAAGTTCGATCTGGTGCCCGTGCCACCAACCTTTATGGAGACTTCTTCACGGGCGACGCCTACG
TCATCCTGAAGACAGTGCAGCTGAGGAACGGAAATCTGCAGTATGACCTCCACTACTGGCTGGGCAATGAGTGCA
GCCAGGATGAGAGCGGGGCGGCCGCCATCTTTACCGTGCAGCTGGATGACTACCTGAACGGCCGGGCGCTGCAGC
ACCGTGAGGTCCAGGGCTTCGAGTCGGCCACCTTCCTAGGCTACTTCAAGTCTGGCCTGAAGTACAAGAAAGGAG
GTGTGGCATCAGGATTCAAGCACGTGGTACCCAACGAGGTGGTGGTGCAGAGACTCTTCAGGTCAAAGGGCGGC
GTGTGGTCCGTGCCACCGAGGTACCTGTGTCTGGGAGAGCTTCAACAATGGCGACTGCTTCATCCTGGACCTGG
GCAACAACATCCACCAGTGGTGTGGTTCCAACAGCAATCGGTATGAAAGACTGAAGGCCACACAGGTGTCCAAGG
GCATCCGGGACAACGAGCGGAGTGGCCGGGCGGAGTGCACGTGTCTGAGGAGGGCACTGAGCCCGAGGCGATGC
TCCAGGTGCTGGGCCCCAAGCCGGCTCTGCCTGCAGGTACCGAGGACACCGCCAAGGAGGATGCGGCCAACCGCA
AGCTGGCCAAGCTCTACAAGGTCTCCAATGGTGCAGGGACCATGTCCGTCTCCCTCGTGGCTGATGAGAACCCT
TCGCCCAGGGGGCCCTGAAGTCAGAGGACTGCTTCATCCTGGACCACGGCAAAGATGGGAAAATCTTTGTCTGGA
AAGGCAAGCAGGCAAAACGAGGAGAGGAAGGCTGCCCTCAAAAACAGCCTCTGACTTCATCACCAGATGGACT
ACCCCAAGCAGACTCAGGTCTCGGTCTTCCTGAGGGCGGTGAGACCCCACTGTTCAAGCAGTTCTTCAAGAACT
GGCGGGACCCAGACCAGACAGATGGCCTGGGCTTGTCTACCTTTCCAGCCATATCGCCAACGTGGAGCGGGTGC
CCTTCGACGCCGCCACCCTGCACACCTCCACTGCCATGGCCGCCAGCACGGCATGGATGACGATGGCACAGGCC
AGAAACAGATCTGGAGAATCGAAGGTTCCAACAAGGTGCCCCGTGGACCCTGCCACATATGGACAGTTCTATGGAG
GCGACAGCTACATCATTCTGTACAACCTACCGCCATGGTGGCCGCCAGGGGCAGATAATCTATAACTGGCAGGGTG
CCCAGTCTACCCAGGATGAGGTGCGCTGCATCTGCCATCCTGACTGCTCAGCTGGATGAGGAGCTGGGAGGTACCC
CTGTCCAGAGCCGTGTGGTCCAAGGCAAGGAGCCCGCCACCTCATGAGCCTGTTTGGTGGGAAGCCCATGATCA
TCTACAAGGGCGGCACCTCCCGCGAGGGCGGGCAGACAGCCCCTGCCAGCACCCGCCTCTTCAGGTCCGCGCCA
ACAGCGCTGGAGCCACCCGGGCTGTTGAGGTATTGCCTAAGGCTGGTGCCTGAAGTCCAACGATGCCTTTGTTT
TGAAAACCCCCCTCAGCCGCCTACCTGTGGGTGGGTACAGGAGCCAGCGAGGCAGAGAAGACGGGGGCCAGGAGC
TGCTCAGGGTGCTGCGGGCCCAACCTGTGCAGGTGGCAGAAGGCAGCGAGCCAGATGGCTTCTGGGAGGCCCTGG
GCGGGAAGGCTGCCTACCGCACATCCCCACGGCTGAAGGACAAGAAGATGGATGCCCATCCTCCTCGCCTCTTTG
CCTGCTCCAACAAGATTGGACGTTTTGTGATCGAAGAGGTTCTTGGTGAGCTCATGCAGGAAGACCTGGCAACGG
ATGACGTGATGCTTCTGGACACCTGGGACCAGGTCTTTGTCTGGGTTGGAAAGGATTCTCAAGAAGAAGAAAAGA
CAGAAGCCTTGACTTCTGCTAAGCGGTACATCGAGACGGACCCAGCCAATCGGGATCGGCGGACGCCCATCACCG
TGGTGAAGCAAGGCTTTGAGCCTCCCTCCTTTGTGGGCTGGTTCCTTGGCTGGGATGATGATTACTGGTCTGTGG
ACCCCTTGGACAGGGCCATGGCTGAGCTGGCTGCCTGAGAGGGGGCAGGGCCACCCATGTACCGGTGAGTGCC
TTTTGGAAGTGTCTTCCCTCAAAGAGGCCTTAGAGCGAGCAGAGCAGCTCTGCTATGAGTGTGTGTGTGTGT
GTGTTGTTTCTTTTTTTTTTTTTTACAGTATCAAAAATAGCCCTGCAAAAATTCAGAGTCCTTGCAAAAATTGTC
TAAAATGTCAGTGTTTGGGAAATTAAATCCAATAAAAACATTTGAAGTGTG

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FIGURE 101

MAPHRPAPALLCALSLALCALSLPVRAATASRGASQAGAPQGRVPEARPNMVEHPEFLKAGKEPGLQIWRVEK
FDLVPVPTNLYGDDFTGDAYVILKTVQLRNGNLQYDLHYWLGNECSQDESGAAAIFTVQLDDYLNGRAVQHREVO
GFESATFLGYFKSGLKYKKGGVASGFKHVVPNEVVVQRLFQVKGRRVVRATEVPVSWESFNNGDCFILD LGNNIH
QWCGSNSNRYERLKATQVSKGIRDNERSGRARVHVSEEGTEPEAMLQVLGPKPALPAGTEDTAKEDAANRKLAKL
YKVSNGAGTMSVSLVADENPFAQGALKSEDCFILDHGKDGKIFVWKGKQANTEERKAALKTASDFITKMDYPKQT
QVSVLPEGGETPLFKQFFKNWRDPDQTDGLGLSYLSSHIANVERVPFDAATLHTSTAMAAQHGMDDDG TGQKQIW
RIEGSNKVPVDPATYQQFYGGDSYIILYNRYRHGGRQGGQI IYNWQGAQSTQDEVAASAILTAQLDEELGGTPVQSR
VVQGKEPAHLMSLFGGKPMI IYKGGTSREGGQTAPASTRLFQVRANSAGATRAVEVLPKAGALNSNDAFVLKTPS
AAYLWVG TGASEAEKTGAQELLRVLRAQPVQVAEGSEPDGFWEALGGKAAYRTSPRLKDKKMDAHP PRLFACSNK
IGRFVIEEVP GELMQEDLATDDVMLLD TWQVFVWVGKDSQEEEKTEALTS AKRYIETDPANRDRRTPI TVVKQG
FEPPSFVGWFLGWDDDYWSVDPLDRAMAELAA

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FIGURE 102

GTTTCTCTCCCTGCCCCGCGACTTCGCGCAAGATCCGGGAAGGACACCCGAGGCCCTGGGAGACCCTGGGGAG
GTGAAAGTCAGAGAGCGAAGCGGGCCGTGGCCCCCTAGGCCTGACCCCTCCCCGCGGGGTAAAGGCGGGCACCCCGC
GAGCGCAGGGGTCTTCTTACTGCTGATGGCACCCAGCTCTGGGCCCAGACGCCGCTCACCGTCCACCGCCGGTGC
TGGGTAAAATGTCGGTTCAGGACCTTACCAGGCGGCCACTGGGCCTTCCTCAGCACCATCCGCACCTCCATCCT
ATGAAGAGACAGTGGCTGTTAACAGTTATTACCCACACCTCCAGCTCCCATGCCTGGGCCAACTACGGGGCTTG
TGACGGGGCCTGATGGGAAGGGCATGAATCCTCCTTCGTATTATAACCAGCCAGCGCCCATCCCCAATAACAATC
CAATTACCGTGCAGACGGTCTACGTGCAGCACCCCATCACCTTTTTGGACCGCCCTATCCAAATGTGTTGTCCTT
CCTGCAACAAGATGATCGTGAGTCAGCTGTCCTATAACGCCGGTGCTCTGACCTGGCTGTCCTGCGGGAGCCTGT
GCCTGCTGGGGTGCATAGCGGGCTGCTGCTTCATCCCCTTCTGCGTGGATGCCCTGCAGGACGTGGACCATTACT
GTCCCAACTGCAGAGCTCTCCTGGGCACCTACAAGCGTTTGTTAGGACTCAGCCAGACGTGGAGGGAGCCGGGTGC
CGCAGGAAGTCTTTCCACCTCTCATCCAGCTTCACGCCTGGTGGAGGTTCTGCCCTGGTGGTCTCACCTCTCCA
GGGGGCCCACCTTCATGTCTTCTTTGGGGGAATACGTCGCAAACTAACAAATCTCCAAACCCAGAAATTGC
TGCTTGGAGTCGTGCATAGGACTTGCAAAGACATTCCCCTTGAGTGTGAGTTCACGGTTTCTGCCTCCCTGAG
ACCCTGAGTCCTGCCATCTAACTGTGATCATTGCCCTATCCGAATATCTTCTGTGATCTGCCATCAGTGGCTCT
TTTTTCTGCTTCCATGGGCCTTTCTGGTGGCAGTCTCAAACCTGAGAAGCCACAGTTGCCTTATTTTTGAGGCTG
TTCTGCCCAGAGCTCGGCTGAACCAGCCTTTAGTGCTACCATTATCTTATCCGTCTCTTCCCGTCCCTGATGAC
AAAGATCTTGCCTTACAGACTTTACAGGCTTGGCTTTGAGATTCTGTAAGTGCAGACTTCATTAGCACACAGATT
CACTTTAATTTCTTAATTTTTTTTTTAAATACAAGGAGGGGGCTATTAACACCCAGTACAGACATATCCACAAGG
TCGTAAATGCATGCTAGAAAAATAGGGCTGGATCTTATCACTGCCCTGTCTCCCCTTGTTTCTCTGTGCCAGATC
TTCAGTGCCCTTTCCATACAGGGATTTTTTTCTCATAGAGTAATTATATGAACAGTTTTTATGACCTCCTTTTG
GTCTGAAATACTTTTGAACAGAATTTCTTTTTTTTAAAAAAAACAGAGATGGGGTCTTACTATGTTGCCAGGC
TGGTGTGCAACTCCTGGGCTCAAGCGATCCTTCTGCCTTGGCCTCCCGAAGTGCTGGGATTGCAGGCATAAGCTA
CCATGCTGGGCCTGAACATAATTTCAAGAGGAGGATTTATAAAACCATTTTCTGTAATCAAATGATTGGTGTGAT
TTTCCCATTTGCCAATGTAGTCTCACTTAAAAAAAAAAAAAGAAAAAGAAATGGATAATTTTCTACTGCCTT
TACTTGGGGTTAATGTGATTCTTAAACACCTTCATCATGGAACCTCTCAGAGTGGGGTCCGTTTTGGTTTCTGCT
GGTGGGTTTTGAAAGATAAGGGAAAGCACATTTTGAGCATGTCTGGGTACCATGGTGCAGGATGCTTGGGAACCAG
AACTGTTTCAGAGGAATCTAAAGTCTGATTTTAGTTTTTTCAGAGACACAGCTTGTTGTAAAACATGAGAAGACATG
ATTTCTAGGACTCAAGCAGCAAGCCAGGATTTAGGTTGGCTGCTGTGTCATCTTTGAAGTCAAGACAAAGCTGG
GCTCGACCTTCAAGGGTCTCGTTTTGATAATACTTCAGAATAGGGAACTCATGTGAATACTACTATGTAGAAAT
AAAACCTAGACCTTGAGCGAACATCTGTATATTGGTTGAAAACGATAGTGGTAACCATTGATCCCCCTTCATTG
ATGTTTGGAAAAATCCAGTAATTATCATTTTTGCAACGAATATGGATAACCACATAGTACTTTGGTGTACCTGCT
TTTGAAAAATAAAGTCTTTGGTTCACCCGGTAAAAAAAAAAAA